



**HETI**  
HEALTH EDUCATION &  
TRAINING INSTITUTE

# Acute Psychiatric Management

2ND EDITION

Edited by Associate Professor Michael Robertson

HETI | RESOURCE

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## Foreword

A clinical encounter with a patient suffering an acute psychiatric episode is likely to occur early in the career of many junior doctors. For many this is their first experience in the emergency department or in out-of-hours practice. This text is a straightforward guide to management options for acute psychiatric conditions. It will certainly help junior doctors prepare for managing what is often a very stressful situation. It is not often that we have a text written specifically with the NSW public health system in mind. The Editorial Group who prepared this text are all prominent psychiatrists working within NSW mental health services, and they have created an excellent resource for all clinicians involved in psychiatry training. I am pleased that the Health Education and Training Institute (HETI) and HETI's Psychiatry State Training Council have been able to support the Editorial Group in this work. HETI has made this text available to all junior doctors and their supervisors via the HETI website, and I hope that it will help junior doctors manage the care of patients with acute psychiatric conditions confidently.

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## Introduction

The commencement of psychiatric training is a daunting task for any medical officer. Whilst exposure to mental illness and the institutional systems which operate around it may occur during graduate medical training programs and some junior resident medical officer rotations, nothing prepares the new trainee in psychiatry for their many responsibilities in this early phase of their careers.

Didactic content is provided for psychiatric trainees by the NSW Institute of Psychiatry and local training networks, however information on how to provide safe and effective care to people with mental illnesses is invariably acquired in the course of working in acute mental health settings. With this in mind, the contributors to this resource have attempted to provide accessible overviews of the kind of information which might be needed in the course of working in acute adult mental health settings.

This resource is set out in a series of themes. It does not seek to provide a comprehensive reference, nor does it attempt to summarise text-books or the current literature in psychiatry. Each contributor has written a brief account of different topics of relevance to practice in acute adult psychiatry. The style of writing aims to provide the reader with a grasp of the necessary information, which can be absorbed rapidly by the inexperienced psychiatric trainee. Whilst not a manual of 'how to be a registrar', it aims to provide a ready reference to both common and classic challenges in the setting of acute adult mental health.

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# 1



# 1

## Assessment

### LEARNING OBJECTIVES

- Describe the components of a comprehensive risk assessment
- Identify the variables associated with increase risk of adversity
- Formulate a comprehensive management plan based on assessment of risk

## Comprehensive approach to risk assessment

### Introduction

The notion of “risk assessment” is usually considered the process of estimating the likelihood of dangerousness, such as completed suicide or harm to others. In the insurance industry, actuarial assessment is a mathematical discipline aimed at computing a probability of adversity, based upon a broad consideration of variables. Such an approach has been applied in criminology in the prediction of recidivism in sexual offences<sup>1</sup>. Actuarial approaches to risk assessment in psychiatry attempt to integrate different situational and clinical factors in different populations at different times<sup>2</sup>. Actuarial approaches have been challenged by their aims to predict, rather than anticipate and prevent dangerousness in psychiatry<sup>3</sup>. The actuarial approach to risk assessment provides little more than passive prediction<sup>4</sup> and is inferior to a standardised clinical assessment<sup>5</sup>. The apparent superiority of clinical judgement appears to relate to its emphasis upon prevention, rather than prediction. The distinction between prevention and prediction is important, in that a recent UK review indicated that whilst around 28% of dangerousness was predictable, 65% was preventable<sup>6</sup>. The clinical approach to risk assessment is also more appropriate in psychiatry, as it links the clinical tasks of gathering data, synthesising data and formulating a plan of action to alter the factors likely leading to a dangerous act on the part of a person suffering mental illness.

<sup>1</sup> Silver E, Chow-Martin L. A multiple models approach to assessing recidivism: Implications for judicial decision making. *Criminal Justice and Behavior*. 2002; 29: 538–568.

<sup>2</sup> Monhan J. The prediction of violent behavior: Toward a second generation of theory and policy”. *American Journal of Psychiatry*. 1984;141:10-15.

<sup>3</sup> Bauer A, Rosca P, Khawalled R, et al. Dangerousness and risk assessment: the state of the art. *Israel Journal of Psychiatry and Related Sciences*. 2003;40:182-90.

<sup>4</sup> Hart S. The role of psychopathy in assessing risk for violence: conceptual and methodological issues. *Legal and Criminological Psychology*. 1998;3:121-137.

<sup>5</sup> Douglas K, Kropp P. A prevention-based paradigm for violence risk assessment: clinical and research applications. *Criminal Justice and Behaviour*. 2002;29: 617-658.

<sup>6</sup> Munro E, Rumgay J. Role of risk assessment in reducing homicides by people with mental illness. *British Journal of Psychiatry*. 2000;176:116-120.

In this chapter, the approach to the assessment of risk moves this process beyond the short-term estimation of harm to a longer term and broader account of adversity facing the patient, considering many different individual, demographic and situational factors. In this approach, the term “risk assessment” refers to the propensity of an episode of mental illness to create adversity in the life of a patient in a broad array of domains.

<b>Physical or emotional harm</b>
<ul style="list-style-type: none"> <li>• Harm to others</li> <li>• Suicide or deliberate self-harm</li> <li>• Sexual assault or exploitation</li> <li>• Latrogenic insult</li> <li>• Traumatic stress before and during episode of care</li> </ul>
<b>Incomplete recovery</b>
<ul style="list-style-type: none"> <li>• Symptom persistence</li> <li>• Treatment non-adherence</li> <li>• Family or cultural resistance</li> <li>• Co-morbid psychiatric disorder</li> <li>• Post-illness impairment of personality</li> <li>• Brain injury</li> </ul>
<b>Chronicity of impairment</b>
<ul style="list-style-type: none"> <li>• Effect of illness process</li> <li>• Stigma</li> <li>• Incapacity to participate in comprehensive treatment</li> <li>• Problems of access</li> <li>• Effect of lifestyle</li> <li>• Family and social determinants</li> </ul>
<b>Deterioration physical health</b>
<ul style="list-style-type: none"> <li>• Latrogenic complications</li> <li>• Neglect of self care</li> <li>• Problems of access</li> </ul>
<b>Long-term impairment of psychosocial and interpersonal functioning</b>
<ul style="list-style-type: none"> <li>• Vocational impairment or job loss</li> <li>• Relationship disruption</li> <li>• Developmental disruption i.e. of Eriksonian tasks</li> <li>• Existential aspects of illness experience</li> </ul>

Table 1 – The main components to the actuarial approach to risk

**The components of the comprehensive approach to risk assessment**

The main domains of an actuarial approach to risk are outlined in Table 1. The short-term risk of physical or emotional harm is usually the main focus in the acute phase of care. Incomplete recovery, via the persistence of psychiatric disturbance or the development of co-morbid psychiatric or physical disorder, is the usual focus of the ‘post-acute’ phase of care. Chronic disability, the effect of stigma and social disadvantage and the impact of illness on long term social, interpersonal and vocational function, as well as the person’s experience of selfhood. Many components of the risk

assessment are addressed in more detail in other parts of this monograph. This chapter will focus upon assessment of risk of harm to others, risk of incomplete recovery and chronicity of impairment and longer term functioning.

### Assessment of risk to others

Traditionally, there is an expectation of psychiatrists to accurately predict risk. Such an expectation is unrealistic in that the predictive capacity of psychiatrists in regards to future harm perpetrated by their patients has been shown to be low<sup>6,7</sup>, with estimates of accuracy varying from 30-60%<sup>8</sup>. The principle failing of psychiatric risk assessment is a tendency to overstate risk<sup>9</sup>.

Any assessment of the capacity for dangerousness to self or other integrates multiple dimensions of the patient's situation including situational factors in the patient's illness or immediate ecological setting, the pattern of previous dangerousness and the effectiveness of intervention. The strongest predictor of future 'dangerousness' is past dangerousness, but this in itself is a vacuous statement in the absence of consideration of the situational factors involved<sup>10</sup>. (e.g. A patient who becomes aggressive when the intensity of auditory hallucinations increases.) Thus, statements of potential for future dangerousness, rather than a "crystal ball" prediction are more methodologically sound.

The MacArthur risk assessment study<sup>11</sup>, a large scale study of the factors associated with violence (Table 2) identified a number of variables associated with heightened risk of dangerousness –

Variable	Comment
Gender	Men more likely than women to be violent, but the difference was not large. Violence by women more likely to be directed against family members and to occur at home.
Prior violence	All measures of prior violence strongly related to future violence.
Childhood experiences	A history of child abuse or neglect and parental criminality was strongly associated with violent offending.
Neighborhood and race	Some trend of increased risk of aggression towards non-white members of the community, but this diminished when the neighborhood was considered 'disadvantaged'.
Diagnosis	A diagnosis of a major mental disorder – especially a diagnosis of schizophrenia – was associated with a <i>lower</i> rate of violence than a diagnosis of a personality or adjustment disorder. A co-morbid diagnosis of substance abuse was strongly predictive of violence.
Psychopathy	Psychopathy was the strongest risk factor identified.
Delusions <sup>12</sup>	The presence of delusions – or the type of delusions or the content of delusions – was not associated with violence. A generally "suspicious" attitude toward others was related to later violence.
Hallucinations	Hallucinations did not elevate the risk of violence. "Command" hallucinations specifically commanding a violent act increased risk, particularly when the voice is recognisable. <sup>13</sup>
Violent thoughts and anger	Thinking or daydreaming about harming others was associated with violence, particularly if the thoughts or daydreams were persistent. High levels of anger correlated with violence.

Table 2 – Summary of the MacArthur study

<sup>7</sup> Steadman HJ, Cocozza JJ, 1980. "The prediction of dangerousness- Baxtrom: A case study". In: G. Cooke, ed. *The Role of the Forensic Psychologist*. Springfield, Il.: Thomas. (pp. 204-215).

<sup>8</sup> Appelbaum P, Guthrie T. *Clinical Handbook of Psychiatry & the Law*. Philadelphia: Lippincott, Williams & Wilkins. 2007.

<sup>9</sup> Levinson R, Ramsay G. Dangerousness, Stress, and Mental Health Evaluations. *Journal of Health and Social Behavior*. 1979;20:178-187.

<sup>10</sup> Litwack TR. Assessments of dangerousness: Legal, research, and clinical developments. *Administration and Policy in Mental Health*. 1994;21:361-377.

<sup>11</sup> Monahan J, Steadman H, Silver E, et al. *Rethinking Risk Assessment: The MacArthur Study of Mental Disorder and Violence*. New York: Oxford University Press. 2001.

<sup>12</sup> Mullen P. Forensic Mental Health. *British Journal of Psychiatry*. 2000.

<sup>13</sup> Junginger J. Command hallucinations and the prediction of dangerousness. *Psychiatric Services*. 1995;46:911-914.

Based upon the literature and clinical experience it is possible to accumulate a series of variables for risk of harm to others, with the expectation that the more modifiable variables will serve as the basis of a management plan.

The approach to the acute assessment of dangerousness requires consideration of both “static” and “dynamic” risk factors. Static risk factors are the components of a particular patient’s presentation, which are not amenable to intervention, such as age, gender or aspects of a patient’s previous history, such as a past history of violent offending. By contrast, dynamic risk factors are those which are potentially amenable to clinical intervention, such as active psychotic symptoms, problematic living circumstances or substance abuse. In formulating an assessment of the risk of particular patient poses to self or other, consideration of the dynamic factors of risk assessment. Dynamic risk factors may be quite changeable, such as the level of psychotic disturbance or acuity of a crisis in a person’s life, or they may be stable such as personality traits or problematic interpersonal relationships (Table 3).

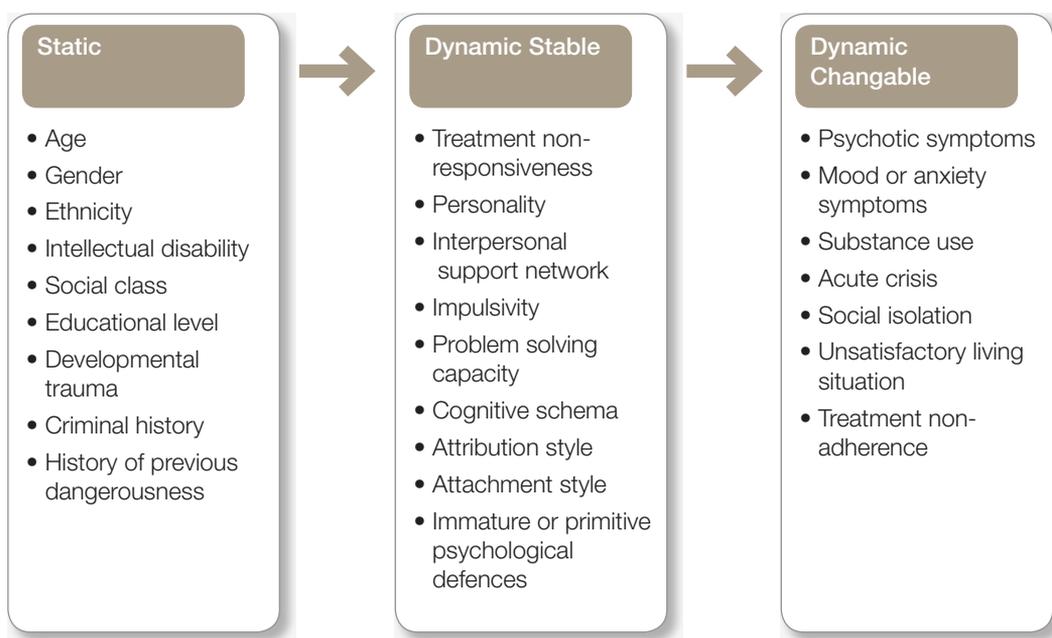


Table 3 – Static and Dynamic Risk Factors

The instrumental value of such an approach is that certain factors amenable to clinical intervention can be identified and implemented, thus potentially reducing risk. Identifying factors historically associated with increased risk of dangerousness in a particular patient serves the basis of a credible risk management plan. For example, a male patient has been previously aggressive in response to command hallucinations, which tend to worsen when there are changes to his living situation and concomitant increase in alcohol use. In this circumstance, the assessing clinician applies the above algorithm and identifies the risk variables of previous aggression, and the relationship of this to increased intensity of psychotic symptoms, alcohol use and disturbed living situation. The risk management plan thus follows along the lines of closer monitoring of psychotic symptoms and further treatment, strategies to avoid or reduce alcohol use and strategies to stabilize the patient’s immediate living situation.

**Psychometric Measurement of risk**

The HCR 20<sup>14</sup> is one of a number of psychometric measures, which assess for the severity of risk, which integrates historical, current clinical and management factors (Figure 2). The HCR-20 has the benefit of being relatively sensitive to change on the clinical and risk-management scales. Other psychometric scales such as the Hare Psychopathy Checklist measure components of potential dangerousness.

<sup>14</sup>. Webster C, Douglas K, Eaves D, Hart S, 1997. HCR-20: Assessing risk for violence (version 2). Burnaby, BC: Mental Health, Law, and Policy Institute, Simon Fraser University.

Items in the HCR-20 Risk Assessment Scheme	
Sub-Scales	Items
<b>Horizontal Scale</b>	
H1	Previous violence
H2	Young age at first violent incident
H3	Relationship instability
H4	Employment problems
H5	Substance use problems
H6	Major mental illness
H7	Psychopathy
H8	Early maladjustment
H9	Personality disorder
H10	Prior supervision failure
<b>Clinical Scale</b>	
C1	Lack of insight
C2	Negative attitudes
C3	Active symptoms of major mental illness
C4	Impulsivity
C5	Unresponsiveness to treatment
<b>Risk Management Scale</b>	
R1	Plans lack feasibility
R2	Exposure to destabilizers
R3	Lack of personal support
R4	Noncompliance with remediation attempts
R5	Stress

Figure 2 – The HCR-20

### Risk of Incomplete Recovery and Chronic Disability

The strongest predictor of prognosis in mental illness is the adequacy of recovery from the index episode. While up to 70% of patients suffering a schizophreniform illness enjoy reduction to mild symptom levels to be classified as having their illness episode remitted, only 20-30% maintain this improvement for 6 months<sup>15</sup>. Incomplete recovery can manifest as symptom persistence, cognitive impairment, the emergence of a comorbid psychiatric or physical disorder or non-specific persisting psychosocial disability. Figure 3 shows the variety of clinical and psychosocial domains in which incomplete recovery manifests. The most frequent instance of incomplete recovery is the incapacity of the person to return to their premorbid level of social, interpersonal and vocational level of function. The persistence of symptoms, albeit in a less severe manner often leads to ongoing psychiatric morbidity. Many patients develop comorbid illnesses, such as 'post-psychotic depression', anxiety or substance misuse disorders. A small percentage of patients will, despite adequate management, experience impairment in attentional or executive dysfunction, which presents an ongoing source of morbidity.

<sup>15</sup> Emsley R, Rabinowitz J, Medori R. Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. *Schizophrenia Research*. 2003;89:129-139.

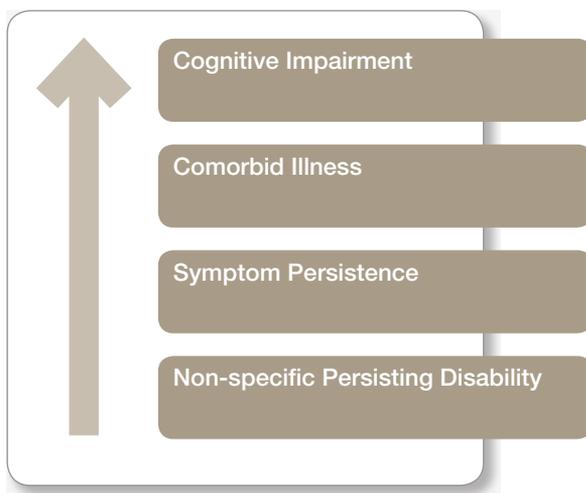


Figure 3 – Clinical manifestation of incomplete recovery.

There are a number of variables associated with incomplete recovery from mental illness (Figure 4).

Intercurrent physical illness, ongoing use of drugs or alcohol and factors intrinsic to the illness process are frequently associated with incomplete recovery from an episode of psychiatric disorder. A patient's incapacity to cope psychologically with the diagnosis and treatment of a severe mental illness, such as propensity for denial or other immature psychological defences can also complicate recovery. Insecure styles of attachment not only result in a greater vulnerability to psychopathology, but can also interfere with the development of a therapeutic alliance with the patient's clinician. Poor social support has long been recognised as a vulnerability factor to psychological distress and psychiatric disorder. Inadequate access to treatment, such as clinical contact, availability of community supervision or even the ability to source appropriate pharmacological or psychosocial treatment are also risk factors for incomplete recovery.

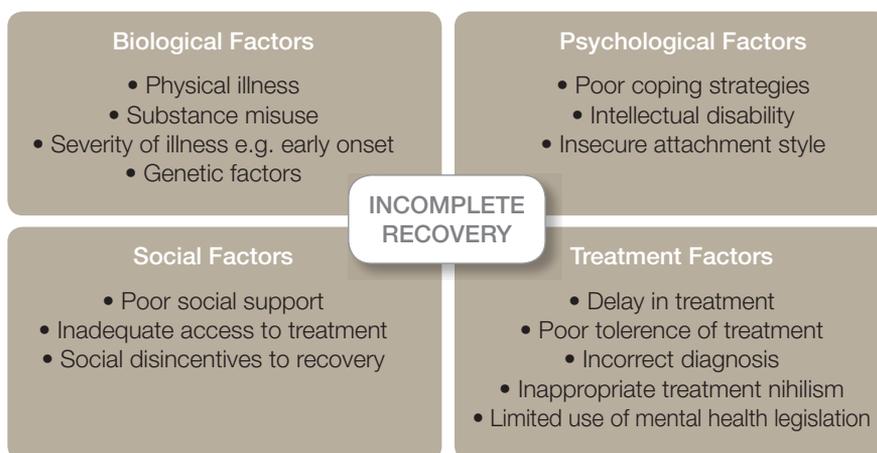


Figure 4 – Risk factors associated with incomplete recovery from mental illness

Moreover, disincentives to recovery in the patient's environment, such as relationship dynamics promoting illness behaviour or other sources of secondary gain must also be considered in formulating a patient's risk of incomplete recovery. The actions of clinicians can also contribute significantly to the risk of incomplete recovery, such as delaying implementation of treatment through incorrect diagnosis, narrow application of legal enforcement of treatment or inappropriate treatment nihilism.

### Long-term impairment of psychosocial and interpersonal functioning

The prospect of chronic psychosocial disability relates to both factors in the illness and the experience of stigma by those suffering mental illness. Wing and Morris (1981) defined this phenomenon as “secondary disability” building upon the primary disability of the disorder itself. Such disability extends from the experience of the illness, in particular “adverse personal reactions” by those around the patient. Tertiary disabilities arise from the “social disablements” borne of broad community responses to people with mental illness<sup>16</sup>.

The notion of stigma is relevant to this process. Stigma, meaning ‘mark’ alludes to the process in which a person with a mental illness is ‘marked’ as different from others by that illness. Erving Goffman described stigma in relation to mental illness as a process of “spoiled identity”<sup>17</sup>. One study found stigma as having multiple components – ‘social distance’, ‘dangerous/unpredictable’, ‘weak not sick’, ‘stigma perceived in others’ and ‘reluctance to disclose’<sup>18</sup>. Despite recent efforts at educating the public about the stigma of mental illness, perceptions of the mentally remain in the realm of “psychokiller / maniac”, “indulgent”, “libidinous”, “pathetic and sad” and “dishonest hiding behind ‘psychobabble’ or doctors”<sup>19</sup>. A survey by SANE Australia found that 76% of consumers and carers experienced stigma at least every few months. Moreover, virtually all people suffering from mental illness believe that negative portrayals of mental illness in the media had a negative effect, in particular, “self-stigma”<sup>20</sup>. The portrayal of mental illness in the media often reflects and perpetuates the myths and misunderstandings associated with mental illness<sup>21</sup>. So severe is the problem, that the World Health Organization and the World Psychiatric Association have identified stigma related to mental illness as the most significant challenge<sup>22</sup>.

The experience of stigma manifests as the propensity of a person with a mental illness to have lower expectations of themselves and their lives, this is particularly the case in seeking employment in an open market<sup>23</sup>. Indeed, unemployment rates for people with serious and persistent psychiatric disabilities are typically 80-90%<sup>24</sup>. Prospective employers are frequently reluctant to hire someone with past psychiatric history or currently undergoing treatment for depression, and approximately 70% are reluctant to hire someone with a history of substance abuse or someone currently taking antipsychotic medication<sup>25</sup>. The experience of such discrimination leads many people with mental illness to view themselves as unemployable and stop seeking work altogether<sup>26</sup>. Figure 5 provides an approach for formulating an assessment of a patient whose illness presents risk of psychosocial disability.

<sup>16</sup> Wing JK, Morris B. Handbook of Psychiatric Rehabilitation Practice. Oxford: Oxford University Press, 1981.

<sup>17</sup> Goffman E, 1963. *Stigma: Notes on the Management of Spoiled Identity*. Engelwood Cliffs, NJ: Prentice-Hall.

<sup>18</sup> Jorm A, Wright A. Influences on young people’s stigmatising attitudes towards peers with mental disorders: national survey of young Australians and their parents. *The British Journal of Psychiatry*. 2008;92:144-149.

<sup>19</sup> Byrne P. Stigma of mental illness and ways of diminishing it. *Advances in Psychiatric Treatment*. 2000;6:65-72.

<sup>20</sup> SANE Australia. Make it Real, 2005. [www.mindframe-media.info/client\\_images/355550.pdf](http://www.mindframe-media.info/client_images/355550.pdf) (accessed April 1 2008).

<sup>21</sup> Hylar SE, Gabbard GO, Schneider I, 1991. Homicidal maniacs and narcissistic parasites: Stigmatisation of mentally ill persons in the movies. *Hospital and Community Psychiatry*. 42:1044-1048.

<sup>22</sup> Sartorius N. The World Psychiatric Association global programme against stigma and discrimination because of schizophrenia. In: Crisp AH, editor. *Every family in the land* [revised edition]. London: Royal Society of Medicine Press. 2004. (pp. 373-375).

<sup>23</sup> Marrone JF, Follwy S, Selleck V. How mental health and welfare to work interact: the role of hope, sanctions, engagement, and support. *American Journal Psychiatric Rehabilitation*. 2005;8:81-101.

<sup>24</sup> Crowther RE, Marchall M, Bond GR, et al. Helping people with severe mental illness to obtain work: systematic review. *British Medical Journal*. 2001;322:204-208.

<sup>25</sup> Scheid TL. Employment of individuals with mental disabilities: business response to the ADA’s challenge. *Behav Sci Law*. 1999;17:73-91.

<sup>26</sup> Link B. Mental patient status, work, and income: an examination of the effects of a psychiatric label. *American Sociol Review*. 1982;47:202-215.

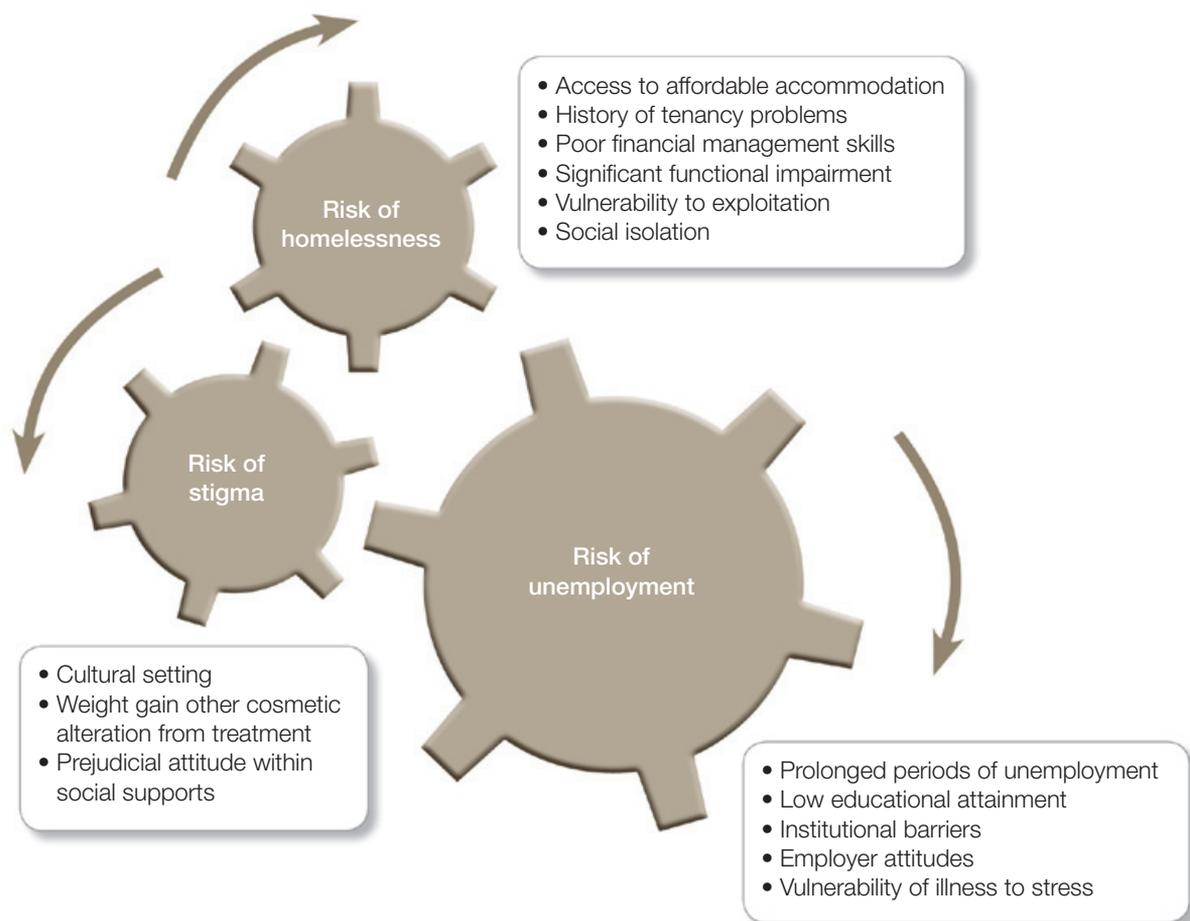


Figure 5 – Approach to formulation of long-term psychosocial impairment arising from a mental illness

In this approach to a patient’s longer term-care, the clinical focus moves beyond identifying acute risk of physical or emotional harm, to identifying the risk of longer-term harm to the patient arising from factors other than their physical safety.

### LEARNING OBJECTIVES

- Understand the nature of suicide attempts and deliberate self harm
- Develop an approach to the assessment of self-harming behaviour
- Formulate a management plan for a patient who has attempted self-harm

## Psychiatric assessment after self-harm

### Introduction

All suicide attempts and expressions of suicidal intent should be taken seriously regardless of whether the individual has made multiple past attempts of low lethality, regardless of the presence of a suspected personality disorder and even if it has been suggested that the attempt was with the aim to manipulate others. At times a patient's suicidal gesture will be described as 'attention-seeking'. This term is often used in derogatory terms and is best avoided as it is likely to negatively influence an otherwise objective risk assessment.

### Suicide and Deliberate Self-harm

There is a view that self-harm attempts can be categorised into 'serious suicide attempts' and more impulsive forms of deliberate self-harm (DSH). The former is typically associated with severe mental illness, high intended lethality and attempts to avoid rescue. The latter is considered a manifestation of personality disorder or acute crisis, where there are impulsive, poorly planned attempts at self-harm. This rule of thumb may be a misleading dichotomy as, regardless of the potential for death or serious injury in the DSH category, the rates of completed suicide years after a seemingly minor episode of so called 'deliberate self-harm' are significant. An example is an Australian study, which followed patients from 1975 onwards. Of those who had made an attempt at deliberate self-harm in the mid 1970's, 4% had completed suicide at 4 years, 4.5% at ten years and 6-7% by 18 years<sup>27</sup>.

### Risk Factors/Aetiology

#### Demographic/Social

There are increased rates of completed suicide and DSH in the elderly and in young males. Men are more likely to complete suicide, whereas women make more attempts. There is an increased suicide risk if a male is widowed, divorced or separated. Other demographic factors that may increase suicide risk include living alone, social isolation, unemployment, financial difficulties and recent legal difficulties. Suicide risk is heightened when there is a family history of suicide or psychiatric illness.

#### Psychiatric

Disorders associated with suicide include:

- Affective disorders – 60% of completed suicides
- Alcohol and drug abuse – 25% of completed suicides
- Psychotic illness – 10% of completed suicides (particularly early in illness course)
- Personality disorders – 5% of completed suicides

Up to 20% of people who complete suicide are intoxicated at the time of their death. Alcohol and drug intoxication affects judgment and impulsivity. The psychological factors associated with suicide include:

- Hopelessness
- Low self-esteem

<sup>27</sup>. de Moore G, Robertson. A Suicide in the 18 Years After Deliberate Self-harm A Prospective Study. *The British Journal of Psychiatry*. 1996;169:489-49.

- Loss experiences
- Conflict
- Bereavement
- Early life trauma

Most importantly, a history of a past suicide attempt is the strongest clinical predictor of a future attempt.

**Medical**

Medical illnesses that have been associated with an increased risk of suicide are shown in Table 1. Suicidal behaviour has been described in association with numerous medical illnesses, some of which are associated with significant morbidity or disability, others which lead to varying states of dysphoria, disinhibition or other neuropsychiatric sequelae. In some circumstances, suicidal behaviour may be induced by the neuropsychiatric adverse effects of treatments for conditions e.g. high dose corticosteroids or chemotherapeutic agents. Infection with HIV may be associated with stigma in some sections of the community, and thus lead to acute states of distress, which may increase the risk of suicide or self-harming behaviour. Frequently, suicidal behaviour emerges out of misunderstanding the illness, its treatment or prognosis.

HIV/AIDS	Cardiopulmonary disease
Head trauma	Peptic Ulcer Disease
Epilepsy	Chronic Renal Failure
Multiple sclerosis	Cushing's Disease
Huntington's Chorea	Rheumatoid arthritis
Organic Brain Syndromes	Cancer
Spinal cord injuries	Chronic pain
Hypertension	

Table 1 – Medical illnesses associated with suicide

**Assessment of attempted suicide and DSH**

**1) Build Rapport**

A patient who is being seen following self-harm or for the assessment of suicidal intent may be distressed, embarrassed or guarded and, therefore, maybe reluctant to engage or cooperate with history taking. However, patients are often relieved by the unburdening of their troubles rather than being annoyed or offended.

**2) Psychiatric History**

Information relating to the attempt or intent should be obtained in an open and direct manner without ambiguity so that mistakes are not made.

It may be helpful to introduce questions regarding suicide in a sequential manner. For example, starting with "With all these problems that you are now facing, have you ever thought that you would rather be dead?" If an affirmative answer is given then it could be asked "Have you ever thought about deliberately ending your life?", then "Have you thought about how you might do this?"

It is often useful to run through a chronological description of the events leading up to, during and after the self-harm or suicide attempt to assess the level of risk.

Features of the history to consider:

**a) prior to self-harm:**

- Significant acute psychosocial stressors (possible precipitating factors) or medical problems
- Low mood or symptoms of a major mental illness
- Feelings of being better off dead
- Feelings of hopelessness
- Drug or alcohol consumption
- Preparation for death; finalising will or life insurance, giving away possessions, writing a suicide note
- Onset of suicidal ideation
- Degree of planning (versus impulsivity)
- The patient's perception of the degree of lethality of the chosen means patient may strongly believe that five sleeping tablets would be lethal in overdose) and the patient's intent (e.g. to die, to escape problems, to sleep)

**b) events at the time of the suicidal act:**

- The setting; where they at home with family around them or did they attempt suicide away from home or at a time when they knew no one would be around
- Was the patient intoxicated?
- Acute stress present? (e.g. argument with partner)

**c) post self-harm:**

- Are they glad or disappointed that they are alive?
- Does the patient show remorse or regret about the attempt? (Shame or regret may be a good or bad thing: some patients will regret the hurt that loved ones may have felt and be less inclined to attempt suicide in the future; a person with low self-esteem may feel even more of a burden or worthless and therefore more determined to carry out further attempts)
- Actions or behaviour after self-harm or suicide attempt (e.g. immediately called someone for help or tried to hide the attempt from others)
- Continued access to suicidal means (e.g. does the security guard who presents after self-harm have access to a gun?)
- Willingness to engage with mental health services and accept treatment
- Ongoing or future suicidal intent or plans
- Plans for the future? Do they express plans to see friends, keep appointments or to try to obtain goals in the future?
- What supports are available in the community?

Has the self-harm served a purpose or helped out the patient in some way (e.g. release of frustration, mobilised the support of loved-ones) that may result in a reduction of risk?

If the patient denies further suicidal intent or plan following an attempt, what has changed? (e.g. an acute stressor has passed, they have come to a realisation that they are loved or that their death would be more significantly felt by others than they previously thought, social supports generated etc.) If there doesn't appear to be any change in the patient's situation following a serious suicide attempt but the patient is denying further suicidal intent then consideration should be given to whether the patient is being deliberately deceptive.

Look for discrepancies in the recall of events that may indicate that the patient is being deceptive (e.g. a patient may present after an 'accidental' injury or overdose in the context of significant psychosocial stressors and have significant risk factors for suicide but denies suicidal ideation or intent) Consider suicidal intent in a patient that has been involved in uncharacteristic risk-taking behaviour; a patient presents obtunded after taking a large amount of benzodiazepines but upon awakening say that their intent was just to get some sleep.

The ability of the patient to guarantee their safety is not a reliable measure of risk.

**d) Past Psychiatric History:**

- Ask about previous suicide attempts; the psychosocial context in which they occurred, the method used, degree of intent and lethality and treatment sought or provided
- It is useful to obtain history regarding the patient's ability to engage with treating professionals or teams
- Presence or absence of diagnosed mental illness or personality disorder

**e) Collateral History:**

It is important to obtain collateral history from past medical files, family, friends, general practitioner, treating psychiatrist or psychologist, or community mental health team

Issues of privacy and confidentiality must be weighed against the level of risk; if the patient does not give consent to talk to third parties, then confidentiality may be broken if it is felt that the level of risk to the patient (or others) outweighs the patient's right to privacy; a judgement may also need to be made about whether there is enough concern to risk jeopardising the therapeutic alliance from contradicting the patient's wishes.

**3) Medical/ Physical Assessment:**

- This will be guided by emergency department or medical staff
- Consider a paracetamol level and other drug screen after self-harm as a routine (not all patients are reliable historians), if the medications ingested are unknown or if there has been a suspected polypharmacy overdose
- Consider a longer period of medical observation for medications with unusual metabolism or those that are slow release
- Patients who are intoxicated with alcohol or other substances may need to be detained in hospital and observed until they are sober so that a more thorough risk assessment can be undertaken
- Assessment of cognitive function may be important as part of an assessment capacity if the patient is requesting to leave or to detect ongoing cognitive side effects of ingested substances.

**Management/ Modification of risk of suicide and DSH****Medical Management:**

- This will be guided by the medical teams
- Sedative medication may be required to reduce distress or reduce risk of harmful behaviour
- It is important that a patient is medically stable prior to being transferred to a psychiatric ward.

**Treatment Setting:**

- Does the patient need to be admitted or could treatment be provided in the community?
  - a. This will depend on the patient's need for medical management, their degree of risk, level of support in the community and their willingness to engage in treatment.
- If the patient is to be admitted should this be as a voluntary patient or under the *Mental Health Act*?
  - a. This will also depend on the degree of risk and the patients level of cooperation with treatment
  - b. The least restrictive environment should be used.
- When a patient is admitted consideration will need to be given to the type of ward and the level of nursing care
  - a. If the patient requires close nursing supervision or is at risk of absconding then it would be appropriate that patient is managed in a closed ward, or observation or high dependency unit
  - b. For patients considered to be of high immediate risk of self-harm consideration should be given to 1:1 nursing care

- c. There may be a lower threshold for 1:1 nursing care on a medical or surgical ward as the expertise of the nursing staff to provide psychiatric care will be low.

**Psychiatric Management/ Modification of Risk Factors:**

- Reduce psychological distress or symptoms
- Increase social support
- Offering alternatives to suicide (e.g. through problem solving techniques)
- Treat underlying psychiatric illness or substance abuse/dependence.

**LEARNING OBJECTIVES**

- Understand the holistic Aboriginal concept of social emotional health and wellbeing of ATSI patients
- Recognise the importance of building rapport and good communication with ATSI patients

## The psychiatric assessment of Aboriginal and Torres Strait Islander peoples

Aboriginal peoples endorse the broader, more holistic concept of social and emotional health and wellbeing rather than mental illness. The separation of mind and body often used in Western mental health is less relevant to Aboriginal peoples. Indigenous perceptions of mental health incorporate the mind, body, spirituality, environment (including relationships with family, land and culture) and socio-political factors, which have contributed to the development of disorder. When one or more of these elements of health is compromised the person may be predisposed to physical or mental problems.

**General principles**

- The centrality of relationships – establishing trust and a genuine connection.
- The consumer is the whole family – who is important? Support and engage them.
- Recognise diversity between and within Aboriginal cultures – avoid assumptions.
- Recognise that history affects current day relationships.
- Adopt a strengths-based approach affirming Aboriginal cultural identity.
- Cultural safety – establish respect, trust and a genuine partnership that values Aboriginal cultural identity, and an environment where people feel safe and empowered to express their cultural identity and may actively participate.

Start interviews by building rapport: be introduced to the patient by a familiar staff member, greet the patient with a loose handshake and brief eye contact, ensure adequate personal space, and give an explanation of who you are and of your role. Hunter advocates starting the interview with a genogram. This helps to quickly establish family relationships, losses, and living arrangements and conveys interest in the patient as a person. It also places the patient in the position of expert. Use non-threatening statements (such as commenting on events within a community or the person's life) to put people at ease. Create a problem list with the patient. This focuses the interview on the patient's priorities. Use humour, especially at your own expense. Keep language simple and clear. Make the patient a cup of tea, a gesture which symbolises hospitality, humility, freeness with time.

**Communication**

- Informed listening: demonstrate an understanding about salient background matters that put the patient's story in a context. Listen to both silences and what is said.
- Use open-ended questions. Indigenous people may feel confronted by direct questioning and give any answer, whether correct or not, in order to deflect attention. It is more important to make a connection with the patient, so talk about things other than the mental health issue first, talk around topics, and accept that not all information may be gathered in one sitting, but that investment in the relationship is most important.

- Talk slowly and wait patiently for a response (quick responses are seen as impolite), and be aware that anxiety about the interview may affect behaviour.
- Particular cultural considerations include not referring to a dead person by name, taboos associated with the use of personal names, recognising that spiritual experiences are not necessarily psychotic, observing cultural norms (e.g. brief or intermittent eye contact, sit beside rather than opposite the patient), checking relationships and sense of belonging to country and family, awareness of the significance of spiritual issues and recognition of the effect of gender of the interviewer (if opposite to the patient, they may feel uncomfortable and unable to disclose information) and transference issues.
- Obtain corroborative information from family, Aboriginal health workers and other involved clinicians and members of the community. Concerns about confidentiality must be weighed up, but obtaining accurate information is important. Clarify which family members are significant and address confidentiality and consent to give information early in the process.

### Mental state examination

The recommendations of Sheldon, Hunter and others are briefly summarised:

**Appearance, behaviour, rapport:** Establishing the patient's usual level of self care may help distinguish what is pathological (for example hygiene, the state of clothing) from normal grooming; recognising that scars may be the result of traditional rituals and not self-harm; appreciating that shyness is common and so avoidance of eye contact may not represent illness.

**Speech:** Responses may be delayed, softly spoken and short. The clinician must also consider the patient's familiarity with English.

**Mood:** If mood is not volunteered, then offering suggestions with words commonly understood in the local community (e.g. "wild" for anger, "silly" for euphoric, "weak" for depressed and "strong" for good or well).

**Affect:** Crying is uncommon as many Aboriginal children brought up traditionally are taught not to cry as it may cause sickness. Shyness and shame may also be mistaken for a flat or depressed affect. A patient may appear blank or expressionless with the clinician and yet be animated and reactive with relatives or familiar people.

**Thought form:** Disturbances of thought form may be more difficult to detect if the patient is not fluent in English. Seek the opinion of relatives, Aboriginal health workers and liaison officers.

**Thought content:** Interpreting the clinical significance of thought content requires awareness of accepted cultural beliefs. Check with the Aboriginal liaison officer or other clinician. For example, in some communities in far North Queensland black magic may be considered a cause of sickness or death and it may be accepted that the spirits of the deceased move around the living and are perceptible at times.

**Perceptual abnormalities:** Fleeting visual hallucinations such as spirits may be reported in the context of intense emotional experiences. However, auditory hallucinations are more likely to indicate mental illness.

**Cognition:** Be aware of biases which may adversely affect performance on Western psychological tests. Check knowledge of familiar material (e.g. sporting teams), observe behaviour in the community (assesses performance in everyday tasks), and check their cognitive reputation (talk to people close to the patient).

**Time:** Aboriginal people often place events in a circular, rather than linear, pattern of time. Events are placed in time according to their relative importance for the individual, with more important events located as 'closer in time'. Assess event/time orientation using culturally and personally relevant events such as 'memory milestones' (e.g. seasons, deaths, and family gatherings). Assess cortical function by having the patient name common objects, copy a drawing of 2 intersecting boomerangs, Luria hand sequences and primitive reflexes.

**Insight and judgement:** Take into account cultural beliefs and norms, including traditional explanations of illness.

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#### LEARNING OBJECTIVES

- Describe the features of depression, anxiety and psychosis in medically ill patients
- Outline investigation and management plans for such presentations

## Psychopathology in the general medical setting

### Introduction

The following provides an overview of assessment and initial management of the medically ill patient in a general hospital setting.

#### *Psychiatric practice in the medical setting:*

- *Referral* – it is important to get a clear idea from the treating team what question is being asked or what is being requested of the psychiatric team; it is helpful to get accurate information regarding the patient's medical illness, management and prognosis as the information will help shape the formulation and guide psychiatric treatment
- *Assessment* – start by reading the patients current and past medical files; check recent medical investigations and the medication chart; when interviewing the patient, initially focus on their medical predicament so that the patient feels their physical complaints are being taken seriously (some patients will feel that a psychiatric referral has been organised as it felt that the patient's problem is in their head); consider the interplay between the patient's coping styles, the medical problem and the psychiatric problem generating the consultation; detailed cognitive testing and assessment of capacity are often required
- *Investigation* – consider further investigations (e.g. TFT, syphilis serology, B12, folate, CT/MRI and gather collateral information)
- *Management* – be aware of drug interactions and how the medical problem(s) may alter the pharmacokinetic or pharmacodynamic properties of the psychotropic medication proposed; consider medications with alternate routes of administration if the patient is nil by mouth or refusing treatment; manage risk; determine whether detainment and treatment is necessary under 'Duty of Care', a Guardianship order or the Mental Health Act; communicate suggestions clearly to the treating team

#### *Interactions between medical and psychiatric problems<sup>28</sup>:*

- Psychiatric presentation of a medical condition or treatment (e.g. delirium)
- Psychiatric reactions to a medical condition (e.g. depression in the setting of cancer)

<sup>28</sup>. Modified from: *Massachusetts General Hospital Handbook of General Hospital Psychiatry*, fifth edition.

- Medical/ physical presentation of a psychiatric condition or treatment (e.g. conversion disorder, metabolic complications of antipsychotic use)
- Comorbid medical and psychiatric conditions (e.g. a patient with schizophrenia is admitted with exacerbation of asthma).

### Depression in the Medical Setting:

#### 1) Epidemiology:

- Prevalence of major depression in elderly inpatients is 10-30%<sup>29</sup>
- Prevalence of depression in inpatients with congestive heart failure 20-37%<sup>30</sup>
- Rate of major depression following myocardial infarction may be as high as 16-23%<sup>31</sup>
- 6 month mortality following MI 17% in depressed group compared to 3% in controls<sup>32</sup>
- 30% of patients depressed after stroke, associated with increased mortality<sup>33</sup>

#### 2) Diagnosis

- Firstly consider whether the patient's predominant symptom is depressed mood, if not the patient may appear depressed or be psychomotor retarded secondary to delirium, dementia or a frontal lobe syndrome, or may have emotional lability secondary to central nervous system disease
- If the patient's mood is depressed then consider whether the depressed mood is a psychological reaction to illness, secondary to a medical problem or a primary psychiatric illness
- Sadness or grief may be appropriate to the situation but a major depressive episode is never appropriate
- Medical conditions commonly associated with depression include:
  - i. pancreatic carcinoma
  - ii. cerebrovascular disease
  - iii. HIV/AIDS
  - iv. Ischaemic heart disease
  - v. Hypothyroidism
- Neurovegetative symptoms are of limited use in depression in the medical setting as they may be the result of a medical illness; however, these symptoms may be useful for diagnostic purposes if they are out of proportion to what would be expected from the medical illness or if a temporal association between the illness and the symptoms is lacking
- Anhedonia is another important symptom; if the patient does not derive pleasure from visits from family or friends then a major depression may be present
- Suicidal ideation may also indicate a major depression.

#### 3) Management

If a major depression is thought to be secondary to a medical illness then consider whether management will involve treating the underlying cause or whether the depression needs to be treated separately.

<sup>29</sup>. Cole MG, McCusker J, Ciampi A, Windholz S, Latimer E, Belzile E. The prognosis of major and minor depression in older medical inpatients. *American Journal Geriatric Psychiatry*. 2006;14(11):966-975.

<sup>30</sup>. Koenig HG. Recognition of depression in medical patients with heart failure. *Psychosomatics*. 2007;48:338-347.

<sup>31</sup>. Schleiffer SJ, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. *Archives Int Med*. 1989;149:1785-1789.

<sup>32</sup>. Roose SP, Glassman AH, Seidman SN. Relationship between depression and other medical illnesses. *JAMA*. 2001;286(14):1687-1690.

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Choice of antidepressant will depend on:

- the most troubling target symptom (e.g. insomnia)
- the side effect profile (e.g. avoid tricyclic antidepressants if cardiac abnormalities are present as these may cause lengthening of PR and QT intervals)
- potential drug interactions (check the effect of the drug on the P450 microsomal enzyme system)

### Anxiety in the Medical Setting

#### 1) *Diagnosis:*

First consider whether the anxiety would be within normal limits for the situation or pathological

The *Massachusetts Handbook for Hospital Psychiatry* makes this differentiation by focusing on the following features:

- Autonomy – “has a life of its own”
- Intensity – the level of distress
- Duration – persistent rather than transient
- Behaviour – avoidance or withdrawal

Pathological anxiety may result from:

- The patient’s reaction to the meaning and implications of medical illness or to the medical setting, based on personality, past individual experiences of the disease or experiences of a loved one, symbolic of early life experiences, conditioned responses
- A physical disorder
- An underlying psychiatric disorder

Medical illnesses mimicking an anxiety disorder:

- Endocrine disorders – Cushing’s syndrome, Addison’s disease, carcinoid syndrome, diabetes, hyperthyroidism, pheochromocytoma, testicular deficiency
- Drug-related – intoxicated (analgesics, antidepressants, chemotherapy, thyroxine, sympathomimetics), withdrawal (alcohol, opiates, benzodiazepines)
- Cardiovascular and circulatory – arrhythmia, mitral valve prolapse, myocardial infarction
- Respiratory – asthma, pneumothorax, pulmonary embolism
- Immunological/connective tissue disorder – SLE, PAN
- Metabolic – acidosis, electrolyte abnormalities
- Neurologic – tumours, syphilis, cerebrovascular disease, encephalopathy, epilepsy, Huntington’s, multiple sclerosis, organic brain syndrome
- Gastrointestinal – peptic ulcer, colitis
- Infectious diseases – AIDS, malaria, tuberculosis, hepatitis
- Miscellaneous – nephritis, nutritional disorders

Clues to a medical cause of anxiety in this population:

- Illness and treatment with known association to symptoms of anxiety
- Presence of physical symptoms with lack of psychological symptoms
- Late onset of anxiety
- A lack of personal or family history of anxiety
- Absence of significant life events heralding or exacerbating anxiety symptoms
- A lack of avoidance behaviour
- A poor response to anti-anxiety agents

#### 2) *Management:*

Anxiety managed with:

- Education – about anxiety and the medical illness (e.g. about misconceptions)
- Support
- CBT
- Medication – the short-term use of benzodiazepines (particularly if there is an immediate need for a response while the patient is in hospital), anti-depressants, atypical antipsychotic for its anxiolytic effects

## Psychosis in the Medically Ill

Medical conditions that can present with psychotic symptoms are shown in Table 1.

1. Epilepsy
2. Head trauma
3. Dementias
4. Cerebrovascular disease
5. Space-occupying lesions – tumours, abscesses
6. Hydrocephalus
7. Multiple Sclerosis
8. Neuropsychiatric disorders – Huntington's disease, Wilson's disease, Parkinson's disease, Friedreich's ataxia
9. Autoimmune diseases – SLE, paraneoplastic syndrome, myasthenia gravis
10. Infections – encephalitis, neurosyphilis, HIV, toxoplasmosis, Cryptococcus infection
11. Endocrine disease – hypoglycaemia, Addison's disease, Cushing's syndrome, hypo and hyperthyroidism, hyper and hypoparathyroidism
12. Narcolepsy
13. Nutritional deficiencies – Mg deficiency, vit A, D, B12 deficiency, zinc deficiency
14. Metabolic disorders – porphyrias
15. Substances – intoxication; alcohol, anabolic steroids, amphetamine, cannabis, cocaine, hallucinogens, inhalants; withdrawal; alcohol, benzo's; medications – anticholinergic agents, antiparkinson meds, chemotherapy, corticosteroids, interferon

Table 1 – Medical illnesses associated with psychotic symptoms

- Assessment requires a medical history, review of systems, family history and physical examination. Cognitive testing should also be performed – deficits in attention, orientation and memory suggest delirium or dementia rather than a primary psychotic illness.
- Consider temporal course – chronic, episodic or recent onset.
- Consider drug-induced psychosis if the psychosis is of new onset, there is no family history or if the psychosis starts in hospital.
- Perform investigations as indicated by clinical index of suspicion.
- Consideration of competency – should the patient be managed under 'duty of care', Guardianship order or the Mental Health Act?

Patients with primary psychotic illnesses can pose problems for nursing staff; e.g. they may be paranoid, disorganised and engage in inappropriate behaviour while on the ward, prominent negative symptoms will make patients seem apathetic or unappreciative and they may have poor hygiene. The psychiatrist may have to explain these difficulties and associate them with their illness rather than personality flaws.

### Management of psychotic patients in a medical setting

- Clarify the diagnosis.
- If an antipsychotic is going to be used, important that this is communicated to the treating psychiatrist or other medical practitioner so that the medication is not continued indefinitely and risk of exposure to side effects in the case of an organic psychotic illness that may have a short duration.
- Watch for dystonias in patients receiving high potency typical antipsychotics (haloperidol) especially in younger patients.
- Be aware of drug interactions and monitor for side effects (e.g. cardiac disturbance).

### LEARNING OBJECTIVES

- Describe the specific mental health needs of LGBTI patients
- Outline the principles of an inclusive approach to the mental health needs of LGBTI patients

## Gay, Lesbian, Bisexual, Transgender and Intersex (LGBTI) patient assessment and health care provision

### Introduction

Lesbian, Gay, Bisexual, Transgender and Intersex (LGBTI) people make up a significant proportion of the Australian population. Approximately 2.5% of males and 2.2% of females self-identify as either homosexuals or bisexual, with 9% of adult men and 15% of women reporting either same sex attraction or sexual experience. Up to 1:1,000 people may be transgender and up to 1:200 intersex. LGBTI people are a part of diverse population groups within Australia, including urban, rural and remote regions, indigenous communities as well as culturally and linguistically diverse groups.

### Background

Homosexuality was only decriminalised in recently in Australia. The first state to pass this was South Australia in 1975 and the last Tasmania in 1997. A number of other legislative changes have also taken place to address discrimination against the LGBTI community. These have included amendments to the age of consent laws, superannuation laws and in more recent time formal acknowledgment of relationships. These changes have paralleled increasing visibility and acceptance of LGBTI people amongst mainstream society. Despite increasing acceptance, LGBTI people continue to face discrimination, marginalisation, family and peer rejection, stigmatisation, harassment and violence. LGBTI people who are migrants or in older age groups may have experienced greater discrimination, marginalisation, harassment and violence as a result of their sexual orientation or gender identity. These experiences negatively impact on people's health and wellbeing.

### LGBTI and Health Outcomes

We know that LGBTI people in Australia have disproportionately negative health outcomes in comparison with the rest of the population. They experience higher rates of depression and anxiety disorders, psychological distress, alcohol, tobacco and other drug use and are more likely to have ever been homeless and to have no contact with family. They also experience higher rates of suicidal ideation and self-harm and are 4 times more likely to have attempted suicide, with even higher rates for transgender people, LGBTI youth and aboriginal people. Reliable mortality statistics for these populations remains highly problematic as sexual orientation, sex identity and gender identity are not identified in most existing data collection mechanism and may not be known by family and friends at the time of death.

Research demonstrates that these negative outcomes are related to the social determinants of health such as discrimination, isolation and marginalisation. These determinants also contribute to barriers to accessing health and support services. In addition, generic health interventions and prevention strategies have failed to be inclusive of LGBTI people and their needs. Social inclusion is recognised as a critical factor in the health and wellbeing of people globally and steps to address this in health and social services is an important step toward reducing the negative impact of the social determinants of health on LGBTI community.

### Formulating a Clinical Approach to LGBTI Patients

A number of recommendations have been made to mainstream providers of health to facilitate an approach that is inclusive of LGBTI people.

- That LGBTI communities be recognised as a higher risk group for depression, anxiety, psychological distress, substance use and suicide.
- Awareness of the social determinants of health which negatively impact LGBTI individuals health and their access to mainstream services.
- Awareness of the potential impact of prior discrimination, harassment, violence, marginalisation or insensitive treatment on LGBTI people. Awareness that LGBTI migrants and individuals from older age groups may have experienced greater exposure to such adverse experiences.
- LGBTI individuals may not have disclosed their sexual preference or gender identity to family, friends, work colleagues or employers because of fear of discrimination or marginalisation. Due attention to the privacy of this information should be taken and not discussed with other parties without the individuals consent.
- Addressing “hetero-centrism” and discrimination against LGBTI people within mainstream services.
- Develop cultural competency of mainstream service providers to provide non-discriminatory, culturally appropriate, inclusive services to the LGBTI community.
- Recognise LGBTI people as individuals rather than as part of a stereotyped group.
- When seeing transgender or gender non conforming persons, use their preferred name, pronoun and terms. If unsure, asking “how would you like to be addressed” or “how would you like me to refer to you” or “which pronoun is appropriate?”
- As with all patients, sensitive questions should be prefaced with an explanation about why the information is needed.
- Consider a collaborative and inclusive approach to service provision through involvement of appropriate LGBTI health services.

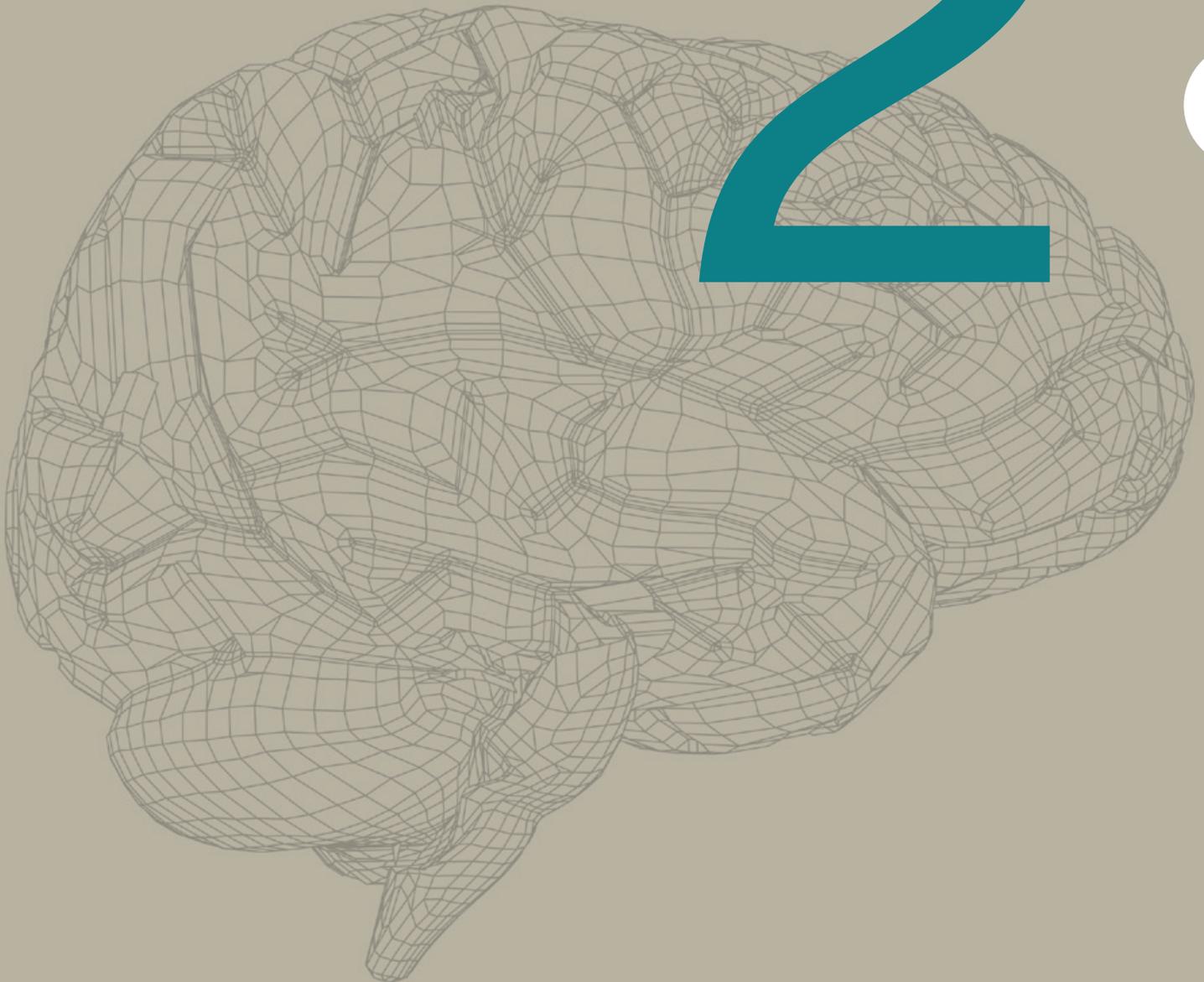
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# 2



# 2

## Treatments

### LEARNING OBJECTIVES

- Describe the various forms of injectable antipsychotics
- Understand the different pharmacological profiles of injectable antipsychotic agents

## Long acting injectable antipsychotics

### Introduction

The advent of long acting injectable antipsychotic medications (LAI) or 'depot antipsychotics' represented a major advance in the ambulatory treatment of patients with chronic psychotic disorders. LAIs enabled clinicians to ensure adherence to treatment and provided patients with greater capacity to live independently in the community. In recent years, technological advances allowing a more sophisticated method of delivery have resulted in several second-generation antipsychotics becoming available as LAIs.

### Pharmacokinetics of LAIs

#### *General Comments*

One of the main advantages of all LAIs is that adherence is more explicit and concerns about covert non-adherence are removed. As LAIs are injected straight into the muscle, they also avoid problems that may occur with absorption from the gut and avoid first pass metabolism. LAIs can produce smoother plasma levels than when the same medication is administered in oral form. This may or may not translate into better tolerability.

#### *Traditional LAI's*

Older LAIs (FGA-LAIs) are manufactured as esters dissolved in oil. In esterified compounds, the active drug forms an ester bond with a long chain fatty acid and the resultant compound is then dissolved in a vegetable oil. Following injection of the oil into the muscle, the esterified drug then slowly diffuses to the edge of the oil globule where plasma esterases cleave the active compound from the long chain fatty acid. The active compound is then able to circulate in the plasma.

Most FGA-LAIs reach a mild peak about 7 days following the injection. One exception to this is fluphenazine decanoate, which has a brief release spike in the first 24 hours after injection. With oil-based LAIs the rate of absorption into the plasma is slower than the rate of elimination. This accounts for the 'flip-flop' kinetics where the time to steady-state is a function of the absorption rate, and the concentration at steady-state is a function of the elimination rate. As absorption can occur over weeks to months, this means that the LAI can continue to have action for months after it is administered. FGA-LAIs can take some months to reach a steady state.

### Microsphere Technology

The first medication to utilize microsphere technology to achieve a prolonged delivery of antipsychotic was Risperdal Consta<sup>®</sup>. This remains the only antipsychotic LAI that utilizes microspheres. Rather than being esterified and dissolved in an oily base, the medication is encapsulated in microspheres made out of a biodegradable copolymer of polyglactin. The microspheres require a chain of cold storage to ensure that they do not begin to break down ahead of administration. After injection into the muscle, the microspheres are slowly eroded and the antipsychotic is then released into the plasma. Very little medication is released from the microspheres until after 2-3 weeks with a peak of release about 4 weeks after injection. The polyglactin is broken down into CO<sub>2</sub> and water.

This method of release gives a very predictable pharmacokinetic profile for release of the medication. However, as almost no medication is released for the first 2-3 weeks after administration, there is a need for oral medication cover during this time. Loading or initiation strategies also cannot be used with this LAI. The LAI must be given at fortnightly basis to maintain consistent levels of the medication and reduce the risk of breakthrough symptoms. Steady state plasma concentrations are not achieved for around 8 weeks.

As a rule 25mg Risperdal Consta<sup>®</sup> fortnightly corresponds to a dose of 2mg oral risperidone daily; 37.5mg Risperdal Consta<sup>®</sup> fortnightly corresponds to 3mg oral risperidone daily; and 50mg Risperdal Consta<sup>®</sup> fortnightly to 4mg oral risperidone daily<sup>34</sup>.

### Crystal-based LAIs

The most recent LAIs to be developed have utilized a crystal-based preparation to deliver the medication. This is a more sophisticated means of delivering the medication that results in the immediate release of medication into the plasma and a much more predictable pharmacokinetic profile.

Olanzapine pamoate was the first antipsychotic to be manufactured as a crystal-based LAI. It consists of a salt of pamoic acid and olanzapine that is suspended in water. The LAI is supplied as a kit that contains 2 vials, one containing powder and one containing a sterile diluent. The diluent is added to the powder and reconstituted just prior to it being injected and the medication is only suitable for gluteal injection. Following injection of the suspension into the muscle, the pamoate salt slowly dissolves releasing olanzapine into the plasma. The slow rate of dissolution of the salt crystals gives the injection its long-acting properties. Release of the medication reaches a peak 2-4 days following the injection, with an apparent half-life of about 26 days. The plasma levels obtained are directly proportional to the dose that is given.

One consideration particular to the olanzapine LAI is the possibility of a post-injection syndrome. This syndrome occurs in a small percentage of people after receiving the injection with signs and symptoms consistent with an olanzapine overdose. The exact mechanism of this syndrome is not completely understood, but is thought to occur by some of the medication crystals coming into direct contact with blood and being absorbed at a faster rate. The syndrome is a risk present every time the injection is given and requires the patient to remain at the health centre for 3 hours of observation following administration.

Dosing of olanzapine pamoate is shown in Table 1.

Daily oral dose olanzapine	Starting dose of olanzapine LAI	Maintenance dose olanzapine LAI >2 months
10mg	210mg/2 weeks or 405mg/4 weeks	150mg/2 weeks or 300mg/4weeks
15mg	300mg/ 2 weeks	210mg/ 2weeks or 405mg / 4 weeks
20mg	300mg/2 weeks	300mg / 2 weeks

Table 1 – dosing of olanzapine LAI

<sup>34</sup> Wilson WA. Visual Guide to Expected Blood Levels of Long-Acting Injectable Risperidone in Clinical Practice. *Journal of Psychiatric Practice*. 2004;10(6):393-401.

Paliperidone palmitate (Invega Sustenna<sup>®</sup>) is the other antipsychotic medication currently available in crystal form. This medication is a LAI form of 9-hydroxyrisperidone, which is the active metabolite of risperidone. Unlike the olanzapine LAI, crystal salts of this medication are supplied already reconstituted in an aqueous suspension in pre-filled syringes. The LAI can be administered in either the deltoid or gluteal muscles, although deltoid administration is recommended for the initiation doses to achieve earlier and higher peak plasma concentrations. Significant release of the active drug from the crystals occurs on the first day following administration and the peak plasma concentration occurs after approximately 2 weeks.

Therapy with Invega Sustenna<sup>®</sup> is initiated with a starting dose of 150mg and a further dose of 100mg 8 days later. 4 weeks later a third dose of 75mg is administered and each subsequent treatment on a 4 weekly basis is titrated. Monthly doses of 50, 75 or 100mg of Invega Sustenna<sup>®</sup> equate to fortnightly doses of 25, 37.5 and 50mg fortnightly of Risperdal Consta<sup>®</sup>. During the period of clinical stabilization, the patient should take oral paliperidone to provide “cover” and their clinical state should be reviewed regularly.

Both the crystal-based LAIs release effective and sustained levels of antipsychotic immediately after injection. Olanzapine LAI and paliperidone LAI also have loading strategies built in to their initiation schedules so that therapeutic plasma levels are achieved quickly and so that oral supplementation is not required.

### Chlorpromazine Equivalents

Chlorpromazine equivalents (CPZe) are a means of comparing the relative potencies of different antipsychotic medications. It must be borne in mind that these equivalencies are an attempt to compare the complex effects of very different drugs. Equivalence doses are generally based on a synthesis of data such as the mean doses used in large populations, the relationship between plasma level and effect, the relationship between dose and plasma level and PET imaging showing D2 receptor occupancy and effect<sup>35</sup>. The following table from the TRS Consensus guidelines<sup>36</sup> combines some of the currently accepted consensus values for CPZe.

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<sup>35</sup>. Lambert T, Taylor J, 2011. Pharmacology of antipsychotic long-acting injections. In Antipsychotic Long-acting injections. Oxford University Press.

<sup>36</sup>. Australian Consensus Panel for Treatment-Refractory Schizophrenia. Targeting treatment-refractory schizophrenia: A multidimensional outcomes approach to the diagnosis and management of incomplete recovery 2010; available at: [www.trscensus.com.au](http://www.trscensus.com.au)

Antipsychotic Drug		Dose equivalent to 100mg chlorpromazine (oral)
Amisulpride	(oral)	100mg
Aripiprazole	(oral)	2.5mg
Clozapine	(oral)	100mg
Haloperidol	(oral)	2mg
Olanzapine	(oral)	4mg
Paliperidone	(oral)	1.5mg
Quetiapine	(oral)	150mg
Risperidone	(oral)	1mg
Thioridazine	(oral)	100mg
Trifluoperazine	(oral)	5mg
Ziprasidone	(oral)	40mg
Zuclopenthixol HCl	(oral)	20mg
Flupenthixol Decanoate	(IM)	13mg every 2 weeks
Fluphenazine Decanoate	(IM)	8mg every 2 weeks
Haloperidol Decanoate	(IM)	33mg every 4 weeks
Zuclopenthixol Decanoate	(IM)	67mg every 2 weeks
Risperidone LAI		13mg every 2 weeks
Olanzapine Pamoate LAI		75 mg every 2 weeks; 135mg every 4 weeks
Paliperidone Palmitate LAI		27mg every 4 weeks

Table 2 – Chlorpromazine dose equivalents

## LEARNING OBJECTIVES

- To know the important effects and side effects of lithium
- To be able successfully to commence and maintain lithium treatment

## Lithium therapy

### Introduction

Lithium has well-established efficacy as an antimanic agent and antidepressant in bipolar disorder, and for prophylaxis against mood episodes in bipolar disorder. It is probably more effective than the anticonvulsants in classical bipolar I disorder and in severe mania. It is one of the more effective augmentation strategies in major depression. Around 50% of antidepressant non-responders achieve remission with added lithium. 15% of people with bipolar disorder complete suicide. Only 10% of these deaths occur while the person is taking some form of mood stabiliser. Lithium is the most effective mood stabiliser at preventing suicide<sup>37, 38</sup>. If a patient is having some breakthrough episodes on an anticonvulsant, a change to lithium is warranted.

Each major mood episode worsens the person's functional outcome, has a serious impact on the person's ability to sustain a job, a marriage or other relationship, and increases the probability of developing dementia in old age. Of those who cease lithium after achieving a good response, about 15% become relatively lithium resistant when relapse forces them to recommence it. For these reasons, requests by a patient with established bipolar disorder to have their mood stabiliser reduced or ceased should be firmly resisted. Ceasing lithium quickly (over < 2 weeks) doubles the risk of relapse. Mixed or dysphoric mania, ultrarapid cycling bipolar disorder and personality disorder have a poor response to lithium, compared to anticonvulsants.

### Some important side effects of lithium

**Renal:** There is a fall in GFR and rise in creatinine in around 15% of patients taking lithium in the long term, but this may be related to episodes of toxicity or cardiovascular problems than to lithium per se. It is more controversial whether lithium at a therapeutic blood level can cause permanent renal damage. Renal failure may certainly occur as a result of toxic levels of the drug, however. Lithium also commonly causes a concentrating defect at therapeutic levels, resulting in polyuria, which may progress to diabetes insipidus. Warn patients to drink water for resulting thirst, rather than soft drinks or fruit juice, as these worsen weight gain. Abnormalities in renal function should be referred to a renal physician for investigation, as there are many possible causes.

**Thyroid:** Lithium suppresses the action of the thyroid, including the release of thyroid hormone from the gland. Clinical hypothyroidism occurs in up to 20% of people (especially women) taking lithium for ten years. A larger number have raised TSH with normal T4 (subclinical hypothyroidism)<sup>39</sup>. In the absence of pre-existing or familial thyroid disorder, thyroid function generally recovers on cessation of the drug. It is not necessary to cease lithium due to thyroid suppression. The patient should be warned at commencement that thyroid suppression is a possibility, and thyroxine replacement will be instituted if necessary. Endocrine referral may be of assistance. There is evidence that even subclinical hypothyroidism may destabilise bipolar disorder, and that thyroxine replacement helps in these cases.

**Teratogenicity:** Lithium is pregnancy category D. It causes serious malformations, especially cardiac anomalies such as Ebstein's, in 4-12% of exposed fetuses. 1<sup>st</sup> trimester exposure is especially risky.

<sup>37</sup>. Goodwin, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA*. 2003;290:1467.

<sup>38</sup>. Tondo, et al. Lithium maintenance treatment of depression and mania in bipolar I or bipolar II disorders. *American Journal Psychiatry*. 1998;155:638.

<sup>39</sup>. Perrild, et al. Thyroid function and ultrasonically determined thyroid size in patients receiving long term lithium treatment. *American Journal Psych*. 147:1518-21.

**Other side effects**

1. Fine intention tremor, occasionally so severe as to require cessation of the drug. Propranolol may help in some cases.
2. Significant weight gain (similar to valproate)
3. Cognitive dulling and mild memory impairment in some patients. Beware of confounding with mild depression or hypothyroidism.
4. Hair thinning
5. Acne
6. Benign T-wave flattening on ECG
7. Benign neutrophilia (WCC around  $10.0 \times 10^9$  is common) due to increased mobilisation from bone marrow stores.

**Toxicity**

Lithium is entirely excreted in the urine. Anything that impedes this excretion may cause blood levels to rise to toxic levels. Your patients will need to be warned to avoid:

1. Excessive lithium intake, for example, some patients take extra tablets on “bad days”.
2. Missing blood tests. Regular tests are vital to detect gradually increasing lithium levels.
3. Dehydration, especially in summer. Some patients try to control the polyuria by reducing water intake, with disastrous results. Take extra fluids or reduce dose during severe diarrhoea or vomiting.
4. Medications that block excretion. All NSAIDs (now over-the-counter) can do this, with the exception of aspirin, and should be avoided. Warn the patient to check all prescription medications for interactions before commencing them. Thiazide diuretics (not loop diuretics such as frusemide) can increase lithium levels into toxic range.
5. Lithium toxicity can result in acute or chronic renal failure, seizures, coma, permanent neurotoxicity (especially cerebellar damage) or death. Dialysis is the treatment of choice at levels  $> 3.0\text{mmol/L}$ .

Symptoms include worsening tremor, worsening metallic taste in the mouth, nausea and fatigue, confusion, worsening polyuria and dehydration. Patients with mild symptoms should be advised to seek a trough lithium level within a day or so. Those with severe symptoms should cease taking lithium and present immediately at the emergency department for testing.

**How to prescribe lithium**

**Before commencing:** Take baseline TFTs, EUC and, if relevant,  $\beta\text{HCG}$ . Warn patients about potential side effects, including renal and thyroid, and teratogenicity. Warn a manic patient and their family that post-manic depression is common, and is not the result of the mood stabiliser. They should seek treatment for this, if it occurs, and not cease the medication.

**Dosing:** 250mg lithium carbonate and 450mg slow release forms are available. The slow release form can be helpful in offering once daily dosing if needed to promote compliance or reduce daytime side effects such as tremor, and in reducing the otherwise daunting number of tablets that the patient must take. Start at around 500mg per day and test after 5-7 days, then adjust dose accordingly. Reduce this for the elderly, who have a lower GFR.

**Blood levels:** Blood levels are taken 12 hours post dose. On single daily dosing, the level will be ~20% higher than with bd dosing. Levels should be done at least weekly until the correct level is attained, and continued every 1-3 months in the long term. TFTs and EUC should be done 6 monthly. With bd dosing, aim for a serum lithium of 0.6 for augmentation in major depression, and 0.8 – 1.0 to treat acute mania. Bipolar prophylaxis is achieved for different patients with levels somewhere between 0.6 and 1.0. Titrate to response and side effects for the individual.

**Insufficient Effectiveness:** Check the serum level, as noncompliance is common. If changing to an anticonvulsant, leave lithium in situ until a good level of anticonvulsant is achieved, then taper lithium. If neither class is completely effective, use lithium in combination with one of the anticonvulsants.

## LEARNING OBJECTIVES

- Understand the indications and efficacy of clozapine
- Describe the appropriate monitoring of medical parameters during clozapine therapy

## Clozapine

### Introduction

Clozapine is still the only drug of proven efficacy in treatment-resistant schizophrenia<sup>40</sup>. The significant response of neuroleptic-resistant schizophrenia patients to clozapine validates its efficacy in this group. Clozapine is of proven superiority over first generation antipsychotics<sup>41</sup> and has a response rate of 50% among previously treatment-refractory patients and 76% among treatment-intolerant patients<sup>42</sup>. The benefits of clozapine are seen in reduction of positive and negative symptoms of schizophrenia, as well as reduction in aggression and suicide<sup>43</sup>.

Clozapine is available under special access provisions of the pharmaceutical benefits scheme. Clozapine can only be prescribed by psychiatrists who have registered with an appropriate clozapine patient monitoring service whose remit is to monitor patients receiving clozapine for haematological abnormalities.

### Initiation of Clozapine Therapy

The initiation of clozapine therapy requires the informed consent of the patient, or where appropriate, the Mental Health Review Tribunal. The risks of agranulocytosis, myocarditis and metabolic complications and the steps undertaken to minimise these must be explained to the patient. The patient must then be registered with the CPMS and baseline white cell count (WCC) and neutrophil count (NC) must also be provided. The patient's blood type must also be identified.

### Clinical Work-up for clozapine therapy

Different clinical services have varied protocols for 'clozapine workup' however the common components of such a work up are shown in Table 1.

1. Informed consent and registration with patient monitoring service
2. Weight, abdominal girth, pulse, blood pressure
3. Full blood count and differential blood count
4. Fasting Glucose
5. Fasting Cholesterol and Triglycerides
6. ECG
7. Echocardiogram
8. Troponin and MB fraction Creatine Kinase
9. EEG (where indicated)

Table 1. – Procedure for initiation of clozapine treatment

<sup>40</sup> Baldessarini RJ, Frankenburg FR. A novel antipsychotic agent. *New England Journal Medicine*. 1991;324(11):746-54 and UK clozapine study group. The safety and efficacy of clozapine in severe treatment-resistant schizophrenic patients in the UK. *British Journal Psych*. 1993;150-54.

<sup>41</sup> Kane J, Honigfield G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic; results of a US multicenter trial. *Psychopharmacol*. 1989;99:560-63.

<sup>42</sup> Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *American Journal Psych*. 1994;151:1744-52.

The initiation of clozapine therapy (“Day 1”) requires close monitoring of pulse, blood pressure, and temperature. There are rare instances of cardiovascular collapse described following the first dose of clozapine (6.25-12.5mg). This usually results from massive vasodilation. Isoprenaline infusion is the pressor of choice, as intravenous adrenaline may lead to further hypotension. Many services require inpatient admission for ‘Day 1’, however day-hospital admission is possible, assuming adequate resuscitation facilities are available. Some patients develop ‘flu-like’ symptoms in the initial phases of clozapine therapy, including pyrexia. This is not related to infection and, in the absence of abnormalities in neutrophil count, should not necessitate the cessation of clozapine.

### Medical Review during dose titration

The patient is usually reviewed weekly during the first 18 weeks of treatment. During this period, clozapine therapy is titrated up towards the usual therapeutic doses of 300-600mg per day in divided doses. Dose increments vary from 12.5-50mg per week, depending upon the patient’s tolerance of treatment. Given the severity of illness usually associated with the need for clozapine therapy, there should be careful documentation of the patients progress (Table 2)

1. Recent progress/symptoms
2. Significant mental state features
3. Risk of harm to self or others
4. Current clozapine dose and tolerability/efficacy
5. Blood results
6. Weight (periodic measure of waist circumference)/ BP/Pulse
7. Action plan

Table 2 – Standard Medical entry during first 18 weeks of clozapine therapy

### Clinical monitoring during clozapine therapy

#### a) Haematological

The most clinically significant adverse effect of clozapine therapy is the induction of agranulocytosis in up to 3% of patients. In order to prevent excess morbidity and mortality in clozapine therapy, the CPMS require regular testing of the patient’s white cell count and neutrophil count in order for clozapine therapy to continue. The CPMS requires weekly leukocyte and neutrophil counts for the first 18 weeks of clozapine therapy and monthly for the duration of therapy. A leukocyte count of  $> 3.0 \times 10^9 / L$  or neutrophil count  $> 1.5 \times 10^9 / L$  represents a contraindication to initiation of clozapine therapy, or grounds for closer monitoring or discontinuation of clozapine therapy. A leukocyte count  $< 3.5 \times 10^9$  or neutrophil count  $< 2.0 \times 10^9$  places a patient in the at-risk category (the “amber zone”) and warrants closer haematological monitoring. There have been a variety of postulated mechanisms of agranulocytosis in clozapine therapy, although the most likely cause is a toxic metabolite of clozapine, N-desmethylclozapine<sup>44</sup>. This compound is likely metabolized to an unstable compound which is toxic to haemopoietic precursors of both myeloid and erythroid lineages<sup>45</sup>.

#### Benign ethnic neutropaenia

Benign ethnic neutropaenia (BEN) has been defined as “the occurrence of neutropaenia defined by normative data in white populations, in individuals or other ethnic groups who are otherwise healthy and who do not have repeated or severe infections”<sup>46</sup>. Between 25% and 50% of Africans and some ethnic groups in the Middle East, including Yemenite Jews and Jordanians have BEN. Individuals with BEN have a similar haematological response to infections as do those without BEN and do not show an increased incidence of infections<sup>45</sup>. Low baseline white cell counts have not been associated with agranulocytosis whilst on clozapine treatment and African American’s do not appear to be at higher risk for agranylocytosis<sup>47</sup>.

<sup>43</sup> Meltzer HY. Suicide and schizophrenia; clozapine and the InterSept study. *Journal Clinical Psych.* 1999;60(Suppl 12):47-50.

<sup>44</sup> Gerson SL, Meltzer H. Mechanisms of clozapine-induced agranulocytosis. *Drug Saf.* 1992;7(Suppl 1):17-25.

<sup>45</sup> Gerson SL, Arce C, Meltzer HY N-desmethylclozapine: a clozapine metabolite that suppresses haemopoiesis. *British Journal Haematol.* 1994;86:555-61.

<sup>46</sup> Rajagopal S. Clozapine, agranulocytosis, and benign ethnic neutropenia. *Postgraduate medical journal.* 2012.

<sup>47</sup> Kelly DL, Kreyenbuhl J, et al. Clozapine Underutilization and Discontinuation in African Americans due to Leucopenia. *Schizophrenia Bulletin.* 2007;33(5):1221-1224.

When neutrophil counts fall below predetermined levels, monitoring services require either repeat FBC in the case of “amber” alert, or cessation of clozapine in the case of “red” alert. In instances of BEN, baseline neutrophils may fall in the “amber” or “red” zone. An awareness of the possibility of benign ethnic neutropenia in patients allows collaboration with haematology and clozapine monitoring services and may also prevent unnecessary cessation of clozapine, or facilitate its use in those who would otherwise been deemed inappropriate<sup>45, 46</sup>.

Lithium, known to cause a relative leucocytosis, has been used to increase neutrophil counts in cases of BEN, or in clozapine induced neutropaenia in order to allow ongoing treatment with clozapine<sup>48</sup>. Lithium does not protect against agranulocytosis. Neutrophil counts have been shown to have diurnal variation, characterised by lower counts in the morning. This phenomenon may be amplified by antipsychotic treatment. Case reports of morning pseudoneutropaenia during clozapine have not demonstrated an association with agranulocytosis. In instances of neutropaenia based on morning blood counts, a repeat count taken in the afternoon may prevent inappropriate cessation of clozapine<sup>49</sup>.

#### **b) Cardiac Monitoring**

Clozapine therapy has been associated with a variety of potentially lethal cardiac abnormalities, acute myocarditis and cardiomyopathy. The risk of myocarditis is highest in the first two months of treatment. Cardiomyopathy is rare, but generally occurs later in treatment. Pericarditis and pericardial effusion have also been associated with clozapine treatment. Tachycardia occurs in about 25% of patients and is also a potential indicator of myocardial disease. Persisting tachycardia beyond two months of treatment, or in association with other symptoms of cardiac failure, palpitations or angina pectoris warrant urgent medical review. A minority of clozapine-treated patients show ECG changes similar to those including S-T segment depression and flattening or inversion of T-waves. These may be benign abnormalities, but they also may be an indicator of myocarditis. The appearance of such anomalies warrants urgent cardiologist review. Patients with a history of cardiac illness or abnormal cardiac findings on physical examination should have a cardiology review prior to commencement of clozapine therapy. Cardiac monitoring during clozapine therapy should include:

1. Routine pulse and BP measurement
2. Pre-treatment ECG (serial measurements depending upon clinical indications)
3. Baseline cardiac enzymes – CK-MB, troponin I, troponin T (serial measurements every 6-12 months)
4. Echocardiogram (pre-treatment and annual)

#### **c) Monitoring Clozapine Levels**

Measuring serum clozapine levels is usually done when there is non-response or partial response to treatment, or where there are questions of treatment adherence. In general, therapeutic levels of clozapine are 1.1 µmol/L (350 ng/mL); the literature recommends combined clozapine and norclozapine levels to be >1.3 µmol/L<sup>50</sup>.

Clozapine levels should be checked in the following circumstances:

1. Where patients are on doses above 600mg daily or;
2. Where there are clinical indications of reduced effectiveness suggesting non-adherence or increased metabolism of uncertain origin;
3. Concomitant administration of the following medications (Table 3):

<sup>48</sup>. Paton C, Raadiyya E. Managing clozapine-induced neutropenia with lithium. *Psychiatric Bulletin*. 2005;29:186-188/Focosi D, Azzara A, et al. Lithium and haematology: established and proposed uses. *Journal of Leukocyte Biology*. 2009;85:20-28/Bray A. Ethnic neutropenia and clozapine. *Australian and New Zealand Journal Psychiatry*. 2008;42:342-345.

<sup>49</sup>. Ahokas A, Elonen E. Circadian rhythm of white blood cells during clozapine treatment. *Psychopharmacology*. 1999;144(3):301-2.

<sup>50</sup>. Perry PJ, Miller DD, Arndt SV, et al. “Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients”. *American Journal Psychiatry*. 1991;148:231-235.

Psychotropics		
Sertraline	Phenytoin	Lithium
Citalopram	St John's Wort	Diazepam
Carbamazepine	Phenobarbitone	Haloperidol
Fluoxetine	Risperidone	Valproate
Fluvoxamine	Modafinil	Lamotrigine
Paroxetine		
Social/Recreational		
Caffeine	Nicotine	Grapefruit juice
Anti-infectives		
Ciprofloxacin	Clarithromycin	Rifampicin
Erythromycin	Ketoconazole	Ritonavir
Cardiac		
Lisinopril	Quinidine	
GI		
Cimetidine		
Other		
Disulfiram	Oral contraceptive pill	

Table 3 – Potential Drug Interactions with clozapine

**d) Neurological Monitoring**

Drug induced movement disorders are uncommon with clozapine therapy, however there should be routine examination assessing for obvious abnormal involuntary movements, parkinsonism, and motor restlessness. Seizures occur at a frequency of 1.3% of patients taking clozapine. Seizures tend to occur at low doses (< 300 mg/d) during the titration phase of treatment, and at higher doses (> 600 mg/d) during the maintenance phase. Patients with a history of seizures or epilepsy are more likely to have seizures soon after initiation of therapy, on low doses. Such patients should have pre-treatment EEGs and routine monitoring as indicated by neurologist advice. Arguments exist as to whether patients taking clozapine doses of > 600 mg/day should undergo routine EEG monitoring. This is best individualised until clearer data is available regarding the cost-benefit of such monitoring.

**Other Side effects of clozapine therapy**

Sialorrhea and constipation are very common side effects. Sialorrhea can be mitigated by 0.1% atropine mouthwash. If left untreated, constipation can become a serious problem with potentially fatal outcomes from severe ileus and obstipation. There are isolated reports have been documented of clozapine-associated emergence of obsessive compulsive symptoms, priapism, allergic complications, pancreatitis, toxic hepatitis, elevation in creatinine kinase levels and diabetes-like symptoms.

**Clozapine cessation**

Serious and potentially fatal adverse events mean that it can become necessary in some patients to abruptly cease clozapine. Other patients may become non-adherent with treatment for a range of reasons. Clozapine is the antipsychotic that has the strongest evidence for a withdrawal psychosis developing when the medication is discontinued<sup>51, 52</sup>. The onset of this withdrawal psychosis is

<sup>51</sup>. Moncrieff J. Why is it so difficult to stop psychiatric drug treatment? It may be nothing to do with the original problem. *Med Hypotheses*. 2006;67:517–523.

<sup>52</sup>. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scandinavia*. 2006;114:3-13.

typically within 24-48 hours of the abrupt discontinuation of clozapine. One previous review has suggested that the overall incidence of a supersensitivity psychosis following the abrupt withdrawal of clozapine is around 20%, but the actual incidence is probably higher than this<sup>53</sup>. Psychotic symptoms occurring as a direct result of antipsychotic medication withdrawal can be more extreme than symptoms occurring as part of the natural course of the illness. If clozapine is unable to be recommenced in a timely fashion, this can result in a severe and protracted relapse with an extended time to recovery and poorer outcomes. As part of the planning to commence clozapine, consideration needs to be given to supports that may be necessary to optimise adherence to medication, as poor adherence can potentially worsen outcomes for some patients.

If it is possible to gradually reduce clozapine this should ideally be done at a rate of 25mg every week to reduce the likelihood of a rebound psychosis developing.

### LEARNING OBJECTIVES

- To understand the uses and side effects of anticonvulsants in psychiatry
- To learn the practical steps involved in starting anticonvulsant medication

## Anticonvulsant medications in psychiatry

### Introduction

In psychiatry, anticonvulsants are predominantly used as mood stabilisers in bipolar disorder. They may also be of benefit in controlling aggression, for example in brain damage or mental retardation. There is little evidence to support their use in unipolar depression. Patients poorly responsive to lithium should try an anticonvulsant, and vice versa. A combination of both classes is commonly required for maximum efficacy in preventing episodes.

### Sodium Valproate

Sodium valproate is the anticonvulsant most commonly used in bipolar disorder. Some studies suggest equal efficacy with lithium; others note inferior long-term outcomes such its relative paucity of evidence for a reduction in suicide. It may be superior to lithium for mixed mood states, rapid cycling and other non-classical forms of bipolar disorder, but less effective for severe mania and classic bipolar<sup>54</sup>. The combination with lithium is more effective in preventing mood episodes than either agent alone.

### Side effects

- Usually better tolerated overall than lithium, with less noncompliance.
- Main serious side effect is hepatic failure. This is rare (1 in 20 000), but a benign elevation in transaminases (up to 3 X normal) is common. Mild elevations warrant regular monitoring, with drug cessation if elevation worsens.
- Less cognitive dulling than lithium
- Tremor (additive with lithium tremor in combination)
- Weight gain often significant.
- Hair thinning and deterioration in hair quality often unacceptable to patients.

<sup>53</sup>. Tollefson GD, Dellva MA, Mattler CA, et al. Controlled, double-blind investigation of the clozapine discontinuation symptoms with conversion to either olanzapine or placebo. The Collaborative Crossover Study Group. *Journal Clinical Psychopharmacol.* 1999;19:435-443.

<sup>54</sup>. Nasrallah, et al. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. *Journal Affective Dis.* 2006;95(1-3):69-78.

- Causes polycystic ovarian syndrome (PCOS) in young women, resulting in weight gain, hirsutism, impaired fertility, impaired glucose metabolism, hyperandrogenism. The incidence of this disorder is controversial. Monitor for menstrual irregularity and weight in young women, and refer to gynaecologist if changes occur.
- Serious risk of teratogenicity. Increases risk of spina bifida to 1-4%.

#### *Commencing and monitoring valproate*

Before or at commencement, take baseline LFTs and a  $\beta$ -HCG if relevant. Warn women about teratogenicity and polycystic ovarian syndrome. Warn about rare hepatic failure and other side effects. Warn manic patients and their families that post-manic depression is common, and is not the result of the mood stabiliser. They should seek treatment for this, if it occurs, and not cease the medication.

#### *Dosing*

Gradual (starting with 500mg and increasing to therapeutic dose over 2 or more weeks) or loading (20mg/kg, around 1500mg per day) regimes are safe and generally well tolerated. Loading may provide a faster response in acute mania.

Allow 5 days for steady state to be achieved, then take blood level. Stated therapeutic ranges are for anticonvulsant effect. Levels above 315 mM/L are recommended, but the most effective range in bipolar disorder is unknown – it is best to titrate to clinical effect and side effects.

Dosing usually bid, but can be once daily to improve compliance.

#### *Drug interactions of particular note*

- Increases lamotrigine levels, which can result in Stevens-Johnson syndrome
- Carbamazepine reduces valproate level, while valproate increases carbamazepine level
- Mildly increases clozapine levels. Prevents clozapine seizures.

### **Carbamazepine**

This drug is perhaps underused as a mood stabiliser. Studies suggest equal efficacy with valproate in bipolar disorder, and its long term side effects are often less problematic than those of valproate<sup>55, 56</sup>.

#### *Side effects*

- Rash (in 5-15%), which requires cessation, as rarely this can progress to dangerous rash such as Stevens-Johnson syndrome. Rechallenge after a benign rash may be successful.
- Transient neutropenia is common, agranulocytosis rare.
- Serious risk of teratogenicity, namely spina bifida (1-3%), craniofacial abnormalities or developmental delay.
- Note less weight gain, hair loss and tremor than lithium or valproate.
- Sedation, dizziness or ataxia.
- Hyponatraemia is common. Monitor severity and cease if a significant reduction occurs.
- Can reduce T4 and T3, without changing TSH. Not clinically significant.
- Benign hepatic enzyme elevation may occur. If progressive, cease drug, as serious hepatic toxicity may rarely occur.

#### *Use and interactions*

Warn patients about side effects, especially rash and agranulocytosis, and teratogenicity. If relevant, take a  $\beta$ -HCG level to exclude pregnancy. Warn manic patients and their families that post-manic depression is common, and is not the result of the mood stabiliser. They should seek treatment for this, and not cease the medication.

<sup>55</sup> Post, et al. Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. *CNS Drugs*. 2007;21(1):47-71.

<sup>56</sup> Nasrallah, et al. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. *Journal Affective Dis*. 2006;95(1-3):69-78.

Start at 200mg bid and titrate to clinical effect and side effects. Again, stated therapeutic levels are for anticonvulsant action, and the therapeutic range in bipolar disorder is unknown.

Once daily dosing of the slow release form can be used to increase compliance.

Carbamazepine powerfully induces cytochrome p450 3A4. This results in several common, clinically significant interactions:

- Autoinduction of its own metabolism and a drop in carbamazepine levels with time. This effect is maximal at one month after starting treatment.
- Reduction in blood levels of oestrogen from contraceptives, which can result in pregnancy. Use higher dose OCP or other contraceptive methods.
- Reduction in levels of many antidepressants, antipsychotics and anticonvulsants, among other drugs. Always check for interactions and adjust doses if necessary.

Do not use with clozapine due to the risk of neutropenia.

### Lamotrigine

Studies suggest effectiveness in bipolar depression, either as monotherapy or with an antidepressant, but a relative lack of efficacy in treating or preventing mania. It is therefore often combined with another mood stabiliser to target both mood poles<sup>57</sup>. If rash does not occur, it is generally very well tolerated. Patients find the lack of weight gain or sedation particularly welcome. As is true for the other anticonvulsants, there is little evidence of efficacy in unipolar depression.

#### *Some common interactions*

Valproate, often combined with lamotrigine, greatly decreases its metabolism. Conversely, lamotrigine increases valproate metabolism, causing valproate levels to fall by around 25%. Carbamazepine slightly increases lamotrigine metabolism, as does sertraline. There is no interaction with lithium.

#### *Important side effects*

- 10% of patients develop rash with lamotrigine. 0.3 – 1% experience serious rash, including Stevens Johnson syndrome, therefore, the drug must be ceased if there is any rash at all.
- A recent large study reports that taking lamotrigine during first trimester is associated with an increased incidence of cleft lip and palate<sup>58</sup>.

#### *Use and dosing*

Rapid escalation of dose increases the incidence of rash, so adherence to a slow commencement protocol is very important. Start at 25mg per day and increase over 6 weeks to 200mg/day (see MIMS for details). A final dose range of 200 – 400 mg is generally used. If the patient is also taking valproate, the above doses must all be halved.

If a patient ceases the drug for more than 5 days, this dosing regime must be recommenced. There is no useful test for serum lamotrigine level, and no blood monitoring is recommended.

### Gabapentin, pregabalin and topiramate

Despite initial hopes, evidence for the effectiveness of these anticonvulsants in mood disorders has unfortunately failed to materialise<sup>59, 60</sup>. They are often of some usefulness in the management of chronic pain, particularly neuropathic pain.

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<sup>57</sup>. Bowden, et al. A placebo controlled 18 month trial of lamotrigine and lithium maintenance treatment recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psych*. 2003;60:392-400.

<sup>58</sup>. Homles, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology*. 2008;70:2152-2158.

<sup>59</sup>. Maidment, ID. Gabapentin treatment for bipolar disorder. *Ann Pharmacotherapy*. 2001;35(10):1264-9.

<sup>60</sup>. Chengappa, et al. The evolving role of topiramate among other mood stabilisers in the management of bipolar disorder. *Bipolar Disorder*. 2001;3:215-32.

**LEARNING OBJECTIVES**

- Describe the various iatrogenic risks of psychotropic agents
- Identify psychotropic treatment regimes which are comparatively safe in pregnancy
- Identify psychotropic agents which are comparatively safe to use in lactating women

**Psychotropic drugs in pregnancy and breastfeeding****Introduction**

As mental illness frequently affects adults in the child-bearing years, the use of psychotropic medications in pregnancy requires closer consideration. This is made difficult by the fact that the information upon which many assumptions are made in this area is based on animal studies and case reports. Moreover, in many instances it is difficult to differentiate a putative teratogenic event related to psychotropic medication and a spontaneous abnormality in an otherwise unremarkable pregnancy, where such instances occur at a rate of 2-3% of all pregnancies carried to term.

**Classifications of medications in pregnancy**

The Australian Therapeutic Goods Administration (TGA) classification of drugs in pregnancy is shown in Table 1. Medications in Category C, D and X raise the most concerns, with the latter two warranting consideration of pregnancy in all female patients in their child bearing years. It is important to note that Category X implies complete contraindication in pregnancy, with many of the other categories based upon lower levels of evidence.

**Category A** – Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

**Category B1** – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

**Category B2** – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

**Category B3** – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

**Category C** – Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

**Category D** – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

**Category X** – Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Table 1 – The TGA Classification of drugs in pregnancy

The current TGA classification for antipsychotic drugs is shown in Table 2.

<p><b>Antipsychotics*</b></p> <p>Category B1 – pimozide, thiothixene</p> <p>Category B3 – quetiapine, ziprasidone, aripiprazole, olanzapine, risperidone</p> <p>Category C – chlorpromazine, fuphenazine, pericyazine, perphenazine, promazine, thiopropazate, thioridazine, trifluoperazine, clozapine, flupenthixol, droperidol, haloperidol, zuclopenthixol</p> <p>Paliperidone – limited data – recommend avoiding</p> <p>* When given in high doses during late pregnancy, related compounds have caused prolonged neurological disturbances in the newborn infant.</p>
<p><b>Antidepressants*</b></p> <p>Category B2 – venlafaxine, mianserin, tranylcypromine</p> <p>Category B3 – Mirtazapine, moclobemide, nefazodone Phenelzine</p> <p>Category C – citalopram, fluoxetine, fluvoxamine, sertraline, amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline, protriptyline, trimipramine</p> <p>Category D – Paroxetine</p> <p>* The use of SSRIs in the third trimester may result in a withdrawal state in the newborn infant.</p>
<p><b>Anticholinergics</b></p> <p>Category A – Procyclidine</p> <p>Category B1 – benzhexol</p> <p>Category B2 – benztropine, biperiden</p>
<p><b>Anticonvulsants/Mood Stabilisers</b></p> <p>Category B1 – gabapentin</p> <p>Category B3 – tiagabine, topiramate</p> <p>Category D – lithium, sodium valproate, carbamazepine, lamotrigine, phenytoin, methylphenobarbitone, phenobarbitone, primidone, ethosuximide, methsuximide, phensuximide, sulthiame, vigabatrin</p>
<p><b>Benzodiazepines</b></p> <p>All Category C</p>

Table 2. TGA Classification of common psychotropic drugs

### Psychotropic Medications at high risk in pregnancy (Category D)

#### Lithium

The potential teratogenicity of lithium is well established. The risk ratio of cardiac anomalies following foetal exposure to lithium is estimated between 1.2-7.7<sup>61</sup>. The UK National Teratology Information Service have concluded that lithium increases the risk of all types of malformation of approximately three-fold and with a weighting towards cardiac malformations of around eight-fold. Whilst septal and valvular defects have been described following fetal exposure to lithium, the classic cardiac malformation is Ebstein anomaly. Ebstein anomaly is characterized by apical displacement of the septal and posterior tricuspid valve leaflets, leading to “atrialization” of the right ventricle with a variable degree of malformation and displacement of the anterior leaflet of the valve. The leaflet

<sup>61</sup>. Cohen L, Freidman J, Jefferson J, et al. A re-evaluation of risk of in-utero exposure to lithium. *Journal of the American Psychiatric Association*. 1994;271:146-150.

anomaly leads to tricuspid regurgitation. The severity of regurgitation depends on the extent of leaflet displacement, ranging from mild regurgitation with minimally displaced tricuspid leaflets to severe regurgitation with extreme displacement. Echocardiogram is the criterion standard for diagnosis. In M-mode echocardiography the finding is typically paradoxical septal motion and dilated right ventricle. There is delayed closure of tricuspid valve leaflets more than 65 milliseconds after mitral valve closure. On two-dimensional echocardiography there is apical displacement of the septal leaflet of tricuspid leaflet of greater than 8 mm/m<sup>2</sup> – considered the most specific sign of the anomaly. Apart from cardiac malformations following first trimester exposure to lithium there are potential dangers towards the end of the third trimester, related to lithium toxicity in the foetus, with case reports of cardiac arrhythmias, cyanosis and hypertonicity. Some studies have also described congenital goitre and neonatal hypothyroidism<sup>62</sup>. Moreover, the rapid shifts in fluid balance following parturition may predispose to lithium toxicity.

### **Paroxetine**

Concerns about the potential teratogenicity of paroxetine are based upon three recent studies. The first, a Danish population based cohort study, found an association between maternal use of SSRIs during the first trimester and an increased risk of both congenital malformations overall (odds ratio 1.4 (95% CI 1.1-1.9)) and congenital cardiac malformations (odds ratio 1.6 (95% CI 1.0-2.6))<sup>63</sup>. The second is a retrospective study conducted by the manufacturer, GlaxoSmithKline (GSK)<sup>64</sup>. The findings suggest that, compared with other antidepressants, paroxetine use during the first trimester is associated with an increased risk of both congenital malformations overall (odds ratio 2.2 (95% CI 1.34-3.63)) and congenital cardiac malformations (odds ratio 2.08 (95% CI 1.0-4.23)). The most common abnormality was ventricular-septal defects, although others were described.

Most recently preliminary information about the results of a new study examining data from a Swedish Medical Birth Registry have been made available<sup>65</sup>. This study suggests that babies born to mothers who have taken paroxetine in the first trimester of pregnancy are at an approximately 2 fold higher risk of congenital cardiac malformations compared with the equivalent frequency in the population (odds ratio 2.22 (95% CI 1.39-3.55)). This study also suggests that the other SSRIs examined (citalopram, fluoxetine and sertraline) are not associated with an increased risk of congenital malformations.

The results of these studies suggest that women should not take paroxetine in the first trimester, and that this does not appear to be an SSRI class effect.

### **Anticonvulsants**

#### **Sodium Valproate**

There is a twenty fold increase in neural tube defects following fetal exposure to valproic acid compounds. A syndrome of specific craniofacial abnormalities and long, thin digits with hyperconvex nails has been described in infants exposed to valproic acid during pregnancy. Valproic acid appears to be associated with a higher risk for major congenital malformations as well as developmental delay and decreased verbal intelligence. These appear to be dose-related.

#### **Carbamazepine**

Prenatal exposure to carbamazepine increases the risk of neural tube defects ten-fold. A syndrome of craniofacial abnormalities, intellectual impairment and hypoplastic nails is described in infants exposed to carbamazepine in utero, Carbamazepine is also associated with a risk of cardiac anomalies.

<sup>62</sup> Williams K, Oke S. Lithium in Pregnancy. *Psychiatric Bulletin*. 2000;24:229-231.

<sup>63</sup> Wogelius P, Nørgaard M, Munk EM, Mortensen PB, Lipworth L, Sørensen HT. Maternal use of selective serotonin reuptake inhibitors and risk of adverse pregnancy outcome (Abstract). *Pharmacoepidemiol Drug Safety*. 2005;14:S72-S73.

<sup>64</sup> <http://ctr.gsk.co.uk/Summary/paroxetine/studylist.asp>.

<sup>65</sup> [www.janusinfo.org](http://www.janusinfo.org)

### Effects of untreated psychiatric disorder in pregnancy

Any treatment decision must be weighed against the deleterious impact of untreated or suboptimally treated psychiatric disorder. Untreated psychiatric disorder imperils the fetus or infant through a variety of risks including poor antenatal care, propensity to nutritional neglect or exposure to toxins or trauma. Moreover, infants under the care of a mentally ill parent are more likely to manifest non-organic failure to thrive or developmental delay, particular cognitive development.

### Guidelines for breast-feeding

Information comes from small case series and single case reports<sup>66</sup>. This limited dataset indicates that all psychotropic drugs are excreted into breast milk and that the infant is therefore exposed to them. In recent decades sufficient data have accumulated to allow psychiatrists to confidently prescribe tricyclic antidepressants, selective serotonin reuptake inhibitors, conventional antipsychotics, carbamazepine and sodium valproate to breast-feeding mothers. There are not sufficient data on newer antipsychotic medications to allow women to breast-feed safely. Clozapine or lithium should not be used in breast-feeding women. Recommended practice is that breast-feeding mothers requiring psychotropic medication be on a low dose of one single drug<sup>66</sup>.

#### **Mother-safe Contact Medications in Pregnancy and Lactation Service**

Phone: 9382 6539 (Sydney Metropolitan Area). Phone: 1800 647 848 (Non-Metropolitan Area)

Fax: (02) 9382 6070 or <http://www.mothersafe.org.au/>

### LEARNING OBJECTIVES

- Describe the current practice of ECT
- Outline the clinical indications for ECT
- List the main adverse effects of ECT

## Electroconvulsive Therapy (ECT)

### Introduction

Whilst ECT is the most controversial and emotive treatment in psychiatry, it is amongst the most effective treatments. Original clinical observations noted that mood and psychotic symptoms often improved following seizures in patients who suffered epilepsy prompted some psychiatrists to experimentally induce seizures in patients in order to clarify their putative benefits. Seizures were induced by chemicals such as camphor and metrazol, however in 1938 – Ugo Cerletti and Lucio Bini induced seizures in patients in their Rome clinic using electrical stimuli. As the ability to induce seizures using electrical stimuli evolved, clinicians introduced muscle relaxants and sedative medications in the practice of ECT. The recent innovations in ECT, including EEG monitoring and more empirically robust approaches to seizure adequacy have seen ECT evolve into a safe and effective physical treatment in severe mental illness.

### The mechanism of action of ECT

ECT involves the delivery of a brief-pulse of square-wave 0.9A AC current (30-70 Hz), across a potential difference of approx. 200V (based upon 220  $\Omega$  impedance across the skull-electrode component of the circuit). The 'width' of the pulse varies from 0.5 – 2 msec and is delivered over duration 0.1 – 8 sec. Both the MECTA and Thymatron ECT machines provide the operator the ability to vary the 'charge' (25 – 504mC) and these variables are automatically computed by the machine. Recent research has suggested that using an ultra brief pulse width with ECT may greatly reduce cognitive side effects, while maintaining efficacy<sup>67</sup>, and this method is used in some specialized

<sup>66</sup>. Kohen D. Psychotropic medication and breast-feeding. *Advances in Psychiatric Treatment*. 2005;11:371-379.

<sup>67</sup>. Loo C, Sheehan P, Pigot M, Lyndon W. A report on mood and cognitive outcomes with right unilateral ultrabrief pulsewidth (0.3 ms) ECT and retrospective comparison with standard pulsewidth right unilateral ECT. *Journal Affect Disord*. 2007;Nov;103(1-3):277-81. Epub 2007 Aug 16.

ECT services. Most stimulus dosing protocols are based upon the variation of the 'charge'. The delivery of the stimulus results in a generalised seizure of between 15 to 180 sec (as noted by EEG). The seizure results from the discharge of different neuronal populations which is paroxysmal, synchronous and repetitive. A period of post-ictal suppression follows the iatrogenic seizure, evident as low amplitude or flat line reading on the EEG. This latter phase appears to be mediated by the GABA mediated discharge of inhibitory interneurons.

The precise therapeutic mechanism of ECT remains uncertain, however ECT is noted to engender down-regulation of beta adrenergic receptors, up-regulation of 5HT<sub>2</sub> receptors, and enhanced activity of GABAergic neurones. In line with recent research into antidepressant efficacy, it is noted that ECT increases the transcription of mRNA coding for neurotrophic peptides such as Brain Derived Neurotrophic Factor, which mediates neurogenesis, arborization and dendritic budding<sup>68</sup>.

Clinically, an increasing seizure threshold during a course of ECT is associated with clinical response. This correlates with the degree of post-ictal suppression on EEG and reflects a likely GABA mediated process.

### Efficacy of ECT

Low-dose unilateral ECT has a response rate of 17%, compared to higher dose unilateral ECT, which has a response rate of 43%. Low dose and high-dose bilateral ECT has a response rate of 63-65%<sup>69</sup>. In the light of this, most clinicians have opted for stimulus-dosing treatment protocols for ECT, in which a patient's seizure threshold is determined empirically, using a titration method of lower charge stimuli, with subsequent treatments being 'dosed' at 2-3 times the established seizure threshold. The strongest predictor of response to ECT in mood disorders is the presence of psychomotor change, particularly psychomotor agitation.

### EEG monitoring in ECT

EEG Monitoring is now standard practice in ECT (Fig. 1-3) The 3 Figures show a typical EEG trace recorded during ECT treatment. A stimulus is delivered and different neuronal clusters discharge paroxysmally, resulting in an EEG trace which is erratic and irregular. This is described as the 'recruitment phase' (Fig. 1). As these discharges summate and become synchronous, the EEG assumes a more uniform appearance, as the seizure occurs and seizure complexes appear (Fig. 2). The seizure leads to the discharge of inhibitory interneurons, which results in a flattened EEG appearance in a phase described as 'post-ictal suppression' (Fig. 3). Note that in all three traces, there is little activity on the EMG, reflecting the administration of muscle relaxants to modify

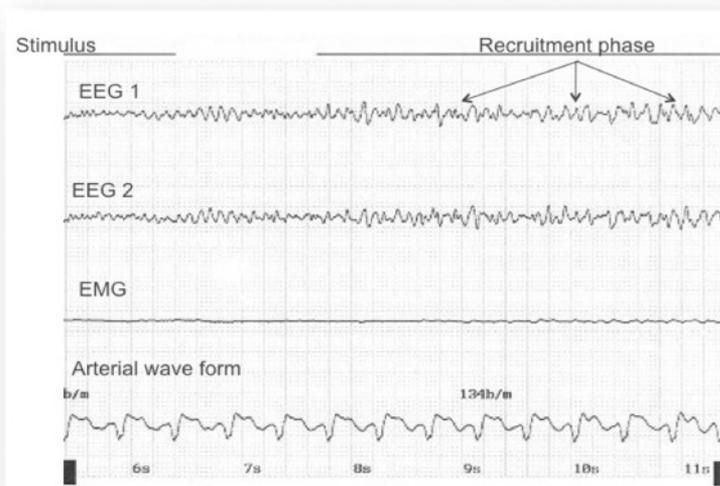


Fig 1. – ECT EEG (trace A)

<sup>68</sup>. Duman RS, Vaidya VA. *JECT*. 1998;14(3):181-193.

<sup>69</sup>. Sackheim HA, et al. *NEJM*. 1993;328:839-846.

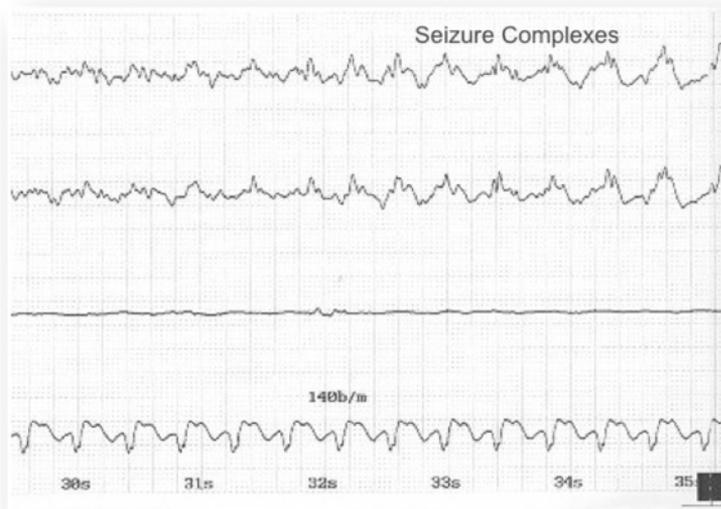


Fig 2. – ECT EEG (Trace B)

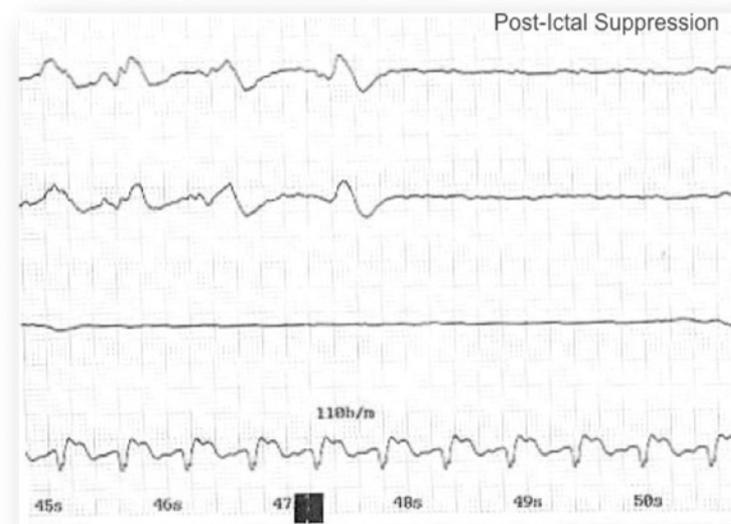


Fig 3. – ECT EEG (Trace C)

the motor component of the seizure. The arterial wave form remains stable in this trace, although there can be alterations in blood pressure post-ictally, mediated by vagal discharge which may lead to bradycardia. Occasionally, there can be a pressor response post ictally, leading to significant hypertension.

### Indications for ECT

ECT is most commonly administered for severe melancholic or psychotic depression, either when antidepressant treatment has been ineffective, or there are severe complications such as refusal to eat or catatonia. ECT is effective in terminating refractory episodes of severe mania and psychotic symptoms in schizophrenia. ECT rapidly reverses catatonic symptoms and may terminate an episode of neuroleptic malignant syndrome or protracted delirium. ECT appears to temporarily alleviate movement disorder in Parkinson's disease and may be used in refractory cases of status epilepticus.

### Adverse effects of ECT

The commonest adverse effects of ECT include transient confusion, headache, nausea, and myalgia. Memory impairment is common during a course of ECT, for both retrograde and anterograde modalities. This is a result of the impairment of working memory. There is no definitive evidence of loss of long-term semantic or episodic memory. Less commonly, ECT can lead to cardiac arrhythmias following the vagal discharge. Hypertension occasionally occurs and can rarely lead to cerebral haemorrhage or stroke. Inadequate muscle relaxation can lead to dental or orthopaedic injuries. Some patients may suffer complications of anaesthesia including aspiration, respiratory suppression or hypoxia. Status epilepticus has been described following administration of ECT. US data indicates a mortality rate of 1 in 80,000 treatments. In the light of this, intracranial lesions such as tumours or known vascular abnormalities represent a contraindication to ECT. Recent myocardial infarction is also a contraindication.

### Treatment course for ECT

Typically, ECT is administered to consenting patients who are medically fit for the treatment. A typical course of ECT is between 6–12 treatments, administered three times per week. In rare instances of psychiatric emergency, treatments are administered daily. Acute treatment is administered until there is sustained clinical improvement and subsequent treatments may be administered less frequently. During a course of treatment, the patient's seizure threshold will increase, necessitating upwards titration of the stimulus level. If ECT is to be administered under the *Mental Health Act*, consent can only be provided by the Mental Health Review Tribunal (MHRT). The MHRT typically require that a case be made as to why ECT is preferred over less invasive treatments. The MHRT also require reports of the patient's clinical progress.

The MHRT rarely approve more than 12 sessions of ECT.

Once a patient has experienced sustained clinical benefit from ECT, progress is maintained using pharmacological treatments. In the case of severe depression, lithium appears to be the most efficacious agent for maintenance of ECT produced remissions. There are some instances, particularly in older patients, where pharmacological treatments are ineffective in maintaining a patient's remission. In such circumstances, the patient may receive maintenance ECT varying from weekly to bimonthly treatments.

### LEARNING OBJECTIVES

- Describe the appropriate indications for prn medication
- Outline appropriate administration of oral prn medication
- Describe procedures for safe administration of parenteral prn regimes

## Pro Re Nata (PRN) medication

### Introduction

Despite the provision of adequate regular psychotropic medication regimes, patients in acute treatment settings frequently experience distress arising from their illness which may increase the risk of harm to the patient, other patients or staff. In such circumstances additional medication regimes are necessary to alleviate the patient's distress and reduce the risk of such harm.

### Indications for prn medication

The administration of prn medication is either initiated by nursing staff or the patient. The common circumstances in which prn medication becomes necessary include:

- Distress arising from psychopathological symptoms
- Agitation arising in the course of an episode of severe mental illness
- Anxiety reactions to psychological phenomena or the ward environment
- Suicidal ideation or impulses to self-harm
- Insomnia
- Physical aggression
- Severe disorganisation of behaviour engendering risk of misadventure
- Intoxication or withdrawal from substances

### Oral prn regimes for agitation or sedation

#### *Benzodiazepines*

Only one type of benzodiazepine should be charted as prn medication:

- Diazepam 5-10 mg orally in a healthy adult every 2-6 hours. Maximum 50 mg in 24 hours (prn and regular)

#### **OR**

- Lorazepam 0.5-1 mg orally every 2-6 hours. Maximum 6 mg in 24 hours (prn and regular).

If underlying agitation is secondary to psychosis and benzodiazepines have not alleviated agitation adequately, antipsychotic medications either as a stat dose or as a prn regimen can be added. If an antipsychotic is the primary (regular) treatment, prn antipsychotic medication charted should match the regular antipsychotic.

#### *Oral neuroleptics*

- Olanzapine wafer or tablets (IM version should not be prescribed on the prn chart but as a statim dose when necessary) 5-10mg orally 2-4 hourly but the total of prn, stat dosing and regular regimen should not exceed 30 mg per day unless the treating psychiatrist has been consulted

#### **OR**

- Quetiapine 25-100 mg orally 2-4 hourly (total maximum of 800 mg/day for regular & prn combined).

### Parenteral regimes for agitation

Intramuscular sedation is indicated when oral medication is not possible or safe for the patient or staff. The aim of parenteral prn medication is to engender a state of rousable sleep (i.e. the patient can be roused and cooperate with directions in response to voice or pain and sleepy if undisturbed) may have to be initiated on occasions.

#### **EITHER**

- Lorazepam 0.5mg-2mg IMI 1-2 hourly, maximum 4mg per day (Peak plasma concentration at 60-90 minutes).

#### **OR (not both)**

- Midazolam 5-10 mg IMI 1-2 hourly, maximum 20 mg per day. Peak plasma concentration in healthy adults 30-60 minutes.

For psychotic/manic agitation not relieved by benzodiazepines

- Haloperidol 5-10 mg IMI 4-6 hourly, total of prn and regular medication is 20 mg a day.

#### **OR**

- Olanzapine 5-10mg IMI 2 hourly (**prescribed as stat doses not as prn**) for patients at risk of EPSE or in antipsychotic naïve patients.

IM Olanzapine should not be given in combination with benzodiazepine or in those who are intoxicated with any substance. There should be a gap of 2 hours between IM benzodiazepines and IM olanzepine because of potential higher risk of respiratory depression. Maximum dose of regular, prn and stat dose of olanzepine should be 30 mg in 24 hours. Concentration peaks 15-45 minutes.

**Zuclopenthixol acetate (Acuphase)** 50-150 mg IM should not be given to any neuroleptic naive patients or be charted as prn medications. It should only be ordered as a stat dose by the medical staff following assessment of the patient's mental state. May be considered for cases where prolonged sedation (eg 2 -3 days) is required and the patient has an established psychotic illness with a high risk of agitation/aggression not managed adequately by any of the above treatments. Peak plasma concentration 24-48 hours with a gradual decline to 1/3 at 72 hours.

Intramuscular ziprasidone mesilate may be used for acute psychotic disturbance. The usual dose is 10-20mg IMI up to a maximum of 40mg daily for no more than three days. If oral ziprasidone is to be used as ongoing antipsychotic therapy, the usual dosing regimes apply (40-80mg bid).

The patient's vital signs and the presence of drug induced movement disorder ought to be monitored at baseline and every 10 minutes (as per local hospital protocol) following sedation for a minimum of 1 hour. The patient must be able to maintain own airway and should be nursed in a way that guarantees the airway remains patent.

If the patient is excessively sedated following prn medication, the patient should be placed in a coma position and continuous oxygen saturation monitor with an ambulatory oxymetry should be made. Blood sugar level should be obtained and thorough physical examination should be carried out. Once it has been determined that the underlying cause is sedation from medication, vital signs such as blood pressure, pulse, respiratory rate, oxygen saturations, temperature and Glasgow Coma Scale should be monitored every 10 minutes for 60 minutes, every 15 minutes for 30 minutes, every 30 minutes for 60 minutes then hourly for 4 hours or until awake. The Medical Officer should not leave the patient for at least 30 minutes and only if the patient could maintain their airway and whose vital signs are stable. Oxygen supplements 6L/minute for healthy individuals, 2L/min for patients with Chronic Obstructive Airway Disease should be provided.

#### *For Acute Dystonia*

Benztropine 1-2mg orally, intramuscularly or intravenously 2-4 hourly maximum 6 mg in 24 hours.

#### **Ethical prescribing practices**

As most prn medication is initiated by nursing staff or patients, the ethical and clinically appropriate use of prn psychotropic medication requires the prescribing medical officer to specify on the patient's medication chart the appropriate circumstances in which such treatment is prescribed and the limits of the dose and frequency of administration of such agents. As much of this occurs in the context of involuntary psychiatric treatment, the appropriate use of prn medication represents a significant ethical issue.

In general terms, prn psychotropic medication is prescribed and administered for either the relief of distress or to reduce the risk of harm to the patient or those around him or her. The decision to use prn medication should only occur once other forms of intervention such as counselling or non-invasive behavioural interventions have been either attempted or at least considered. The use of prn medication to control any form of challenging behaviour, such as harmless acting out or importuning on staff is ethically questionable. Prior to the use of prn medication, it ought to be documented in the patient's file the reasons for such medication and the desired effect. A regime of monitoring desirable and adverse consequences of such treatment should be specified. The consistent administration of prn psychotropic medication beyond 24 hours should warrant prompt review of the adequacy of the patient's routine medication regime.

Apart from considerations of patient safety, the use of prn medication warrants close consideration of the patient's dignity. Such medication should be administered in a respectful and patient manner, away from view of other patients. If a patient is excessively impaired from such treatment, staff should ensure that this impairment does not result in the patient being placed in demeaning or humiliating situations, such as being seen by other patients or visitors to the ward semi-naked or severely affected by such medication. If prn medication requires the use of seclusion or physical restraint, this should be done in isolation from the ward milieu and according to appropriate guidelines for such restraint.



# 3

# 3

## Management Challenges

### LEARNING OBJECTIVES

- Describe the predictors of physical aggression in psychiatric patients
- Outline the pharmacological management of physical aggression in psychiatric patients
- Outline the non-pharmacological management of physical aggression in psychiatric patients

## Acute management of physical aggression

### Introduction

Physical aggression is an infrequent but problematic phenomenon in psychiatric practice. Such incidents can occur in a number of settings, however junior medical staff are usually required to manage them in Emergency Departments and in inpatient settings. Whilst this section outlines general principles of management, each clinical setting may have its own approach to the management of such incidents.

### Determinants of Physical Aggression

Table 1 outlines the indicators of acute risk for physical aggression. As was described in the section dealing with formal risk assessment, there are historical or 'static' indicators and dynamic or 'variable' components. Whilst a history of previous aggression heightens the concern about a particular patient's presentation, it is the observable, cross-sectional features of mental state, which determine the immediate likelihood of physical aggression.

### General Principles of management

Different levels of physical or verbal aggression necessitate different responses. Levels of disturbance can be categorised from 1-3 with appropriate management approaches (Figs 1– 3). In any process of intervention, the medical officer ought take responsibility for their own safety and the safety of other staff including:

- Wearing appropriate attire (e.g. Breakable name tags)
- Access to duress alarms
- Ensuring the patient and staff have a clear means of escape
- Ensuring there are adequate staff available for assistance

Past history of physical aggression
<ul style="list-style-type: none"> <li>• Past aggressive behaviour, severity, use/possession of weapons</li> <li>• Past threats, recent threats</li> <li>• Substance abuse</li> <li>• Past impulsivity</li> <li>• Poor psychosocial supports</li> <li>• Recent severe stress, loss, threat of loss</li> <li>• Past indications/diagnosis of antisocial personality disorder</li> </ul>
Current Symptoms/Mental State
<ul style="list-style-type: none"> <li>• Intoxicated</li> <li>• Cognitively impaired</li> <li>• Psychotic and/or manic</li> <li>• Delusions or hallucinations focussed on a particular person</li> <li>• Command hallucinations</li> <li>• Preoccupation with violent fantasy</li> <li>• Delusions of control (especially with violent themes)</li> <li>• Agitation, excitement, hostile, suspicious</li> <li>• Frustrated, angry</li> <li>• Pacing, yelling, not cooperating</li> <li>• Medical – pain, acutely unwell</li> </ul>

Table 1 – Risk factors for acute aggression

**Level 1** disturbances are characterised by lower levels of physical aggression, reflecting more the patient’s subtle experience of distress. In general, such incidents are best managed by providing the patient a lower stimulus environment and the opportunity to ventilate their distress. Arousal reduction techniques such as deep breathing, mindfulness or progressive muscle relaxation are the best approaches.



Figure 1 – ‘Level 1’ disturbances and their management

**Level 2** disturbances are characterised by more significant agitation, menacing behaviour on the part of the patient including verbal aggression and damage to property. The appropriate management of this level of disturbance includes a combination of recruiting appropriate numbers of staff via a so-called ‘duress’ or emergency call, isolation of the patient from the at risk environment and the appropriate use of oral or parenteral medication to relieve distress (Figure 2).

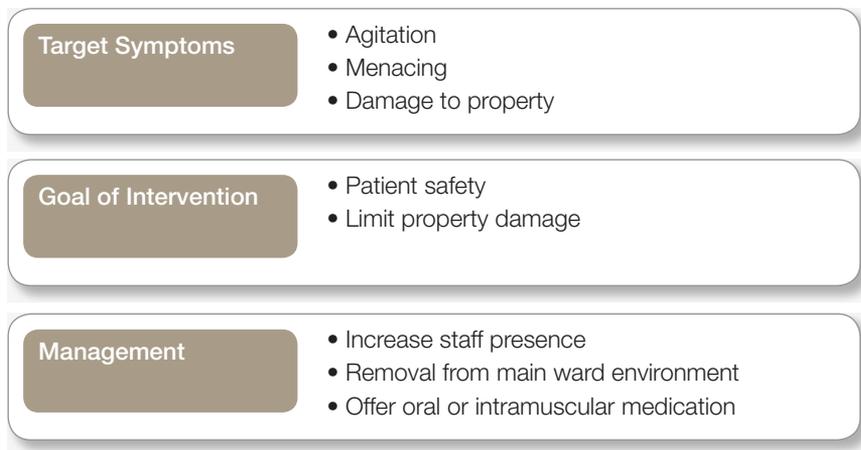


Figure 2 – Level 2 disturbances

**Level 3** disturbances are the most severe, characterised by actual physical aggression or assaultive behaviour. Such patients are often severely distressed by psychotic symptoms or disinhibited by alcohol or other drugs. These instances represent psychiatric emergencies and warrant management including use of physical restraint, seclusion, the administration of parenteral psychotropic medication and the appropriate level of monitoring. The safe restraint of such patients, to protect both staff and the patient from injury, requires special training. Psychotropic medication administered parenterally, particularly when benzodiazepines are combined with antipsychotic medications, may be unpredictable in their effects (Figure 3). Seemingly small doses can lead to catastrophic complications such as upper airway collapse or respiratory arrest. As such, parenteral psychotropic treatment should only be used when adequate resuscitation facilities are available. The patient must be monitored for signs of cardiovascular instability, oxygen desaturation and airway protection. The circumstances of seclusion or administration of emergency parenteral antipsychotic medication require careful documentation in both the patient’s chart and a formal ‘seclusion register’ (a requirement of all Declared Mental Health Facilities).

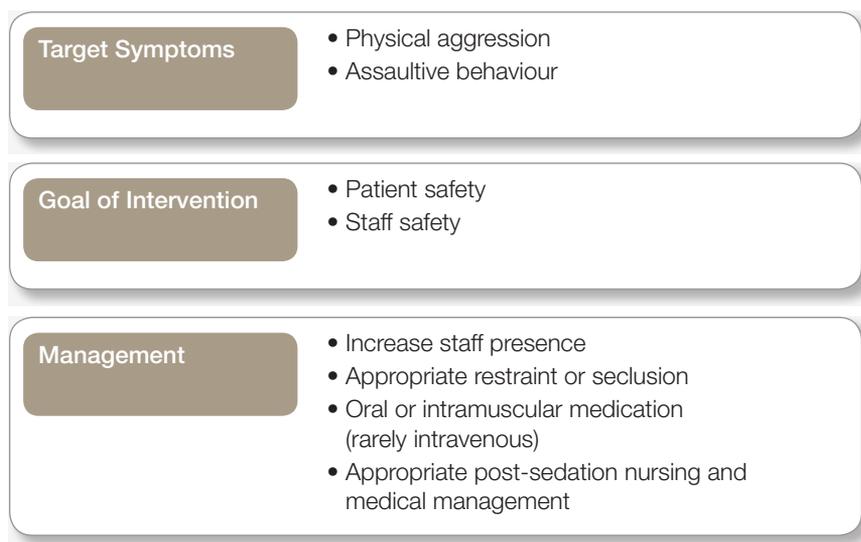


Figure 3 – Level 3 disturbances

**Psychotropic Drug Use in Managing Aggression**

*Oral Regimes* The management of some Level 1 and most Level 2 disturbances involves the use of oral psychotropic medication. In most circumstances, this will involve the use of a benzodiazepine with or without the co-administration of an antipsychotic medication (Table 2).

Benzodiazepines
Lorazepam 0.5-2mg every 6-12 hours
Diazepam 2-10 mg every 12-24 hours
Antipsychotic Medications
Olanzapine 5-10mg
Quetiapine 50-200mg
Haloperidol 2.5-5mg
Risperidone 1-2mg
Chlorpromzine 50-200mg

Table 2 – Oral psychotropic management of aggression

*Parenteral Regimes* The management of Level 3 disturbances often involves the administration of parenteral psychotropic medication (Table 3). As this is largely done via intramuscular injection, only one psychotropic medication is used, to limit the number of injections. In circumstances where these are combined. **PARENTERAL OLANZAPINE SHOULD NOT BE COMBINED WITH BENZODIAZEPINES.**

Benzodiazepines
Lorazepam 0.5-2mg IMI
Midzolam 5-10mg IMI
Antipsychotic Medications
Olanzapine 5-10mg IMI
Haloperidol 2.5-5mg
Clopixol acuphase 50-100mg*
* Care must be taken with neuroleptic naïve patients. Repeated administration of this agent must not exceed 300mg over 4 days

Table 3 – Parenteral psychotropic management of aggression

### LEARNING OBJECTIVES

- Describe the clinical features of alcohol and benzodiazepine withdrawal syndromes
- Outline the pharmacological management of alcohol withdrawal syndromes
- Outline the non-pharmacological management of alcohol withdrawal syndromes

## Acute management of alcohol and benzodiazepine withdrawal syndromes

### Introduction

Abuse of alcohol is a common problem in the community and the hazardous use of alcohol is a clinical challenge encountered frequently in psychiatric practice. Alcohol withdrawal syndromes vary from mild to potentially lethal problems, requiring careful clinical management. Benzodiazepine abuse is less common, however benzodiazepine withdrawal syndromes are often quite severe and frequently missed.

### Alcohol Withdrawal Syndromes

The use of alcohol in the community varies from occasional moderate use to severe alcohol dependence syndromes (Fig .1). 'Social drinking' varies from tee-total to occasional levels of alcohol use within recommended limits i.e. <10 standard drinks per week for men and <5 for women. 'Problem drinking' is evident when the use of alcohol is in a stereotypic pattern, takes a primacy over other activities and results in missed social or vocational responsibilities, legal consequences or behaviour which creates problems for the individual, such a verbal or physical aggression. 'Hazardous drinking' is characterized by evidence of significant complications of alcohol use, such as 'black outs', mild withdrawal syndromes or acute end-organ complications including hepatic steatosis or acute pancreatitis. Harmful drinking sees more established end-organ complications such as peripheral neuropathy, cardiomyopathy, cerebellar damage or early stages of cirrhosis. Alcohol dependence is a distinct syndrome of physiological dependence upon alcohol, requiring increasing use of alcohol in any form to avoid withdrawal.



Figure 1 – Patterns of alcohol use in the community

The physical complications of prolonged severe alcohol use are shown in Table 1.

Neurological	
Cerebral atrophy (especially frontal lobes)	Midline cerebellar atrophy
Korsakov's syndrome	Wernickes' encephalopathy
Peripheral Neuropathy	
Cardiovascular	
Cardiomyopathy	Hypertension
Accelerated dyslipidaemia and atheroma formation	
Gastroenterological	
Hepatic steatosis and steatohepatitis	Malabsorption syndromes
Cirrhosis and portal hypertension	Oropharyngeal cancers
Acute and chronic pancreatitis – malabsorption and diabetes	
Gastritis and gastro-oesophageal reflux	
Reproductive	
Gonadal atrophy	Feminisation in males
Increased risk of breast cancer	

Table 1 – Physical complications of long-term alcohol abuse

### Features of alcohol withdrawal

Alcohol withdrawal can vary in severity from mild discomfort to a severe agitated delirium that has a 10% mortality. In most circumstances, patients will evidence signs of autonomic hyperarousal 12-24 hours after their last drink. This manifests as lability of pulse or blood pressure, tremulousness, diaphoresis or agitation. Untreated these may progress into more florid states of confusion. Some patients may suffer myoclonus or seizures (so-called 'rum fits'). In less than 1-2% of cases, patients enter a phase of alcohol withdrawal delirium, previously termed 'delirium tremens'. Such patients experience vivid and terrifying hallucinosis, psychomotor agitation, disorientation to day or night and formication (crawling skin). If the patient survives, the episode terminates after 36-48 hours and is followed by a prolonged period of somnolence. Death is usually caused by acute renal failure, hepato-renal syndrome, or complications of other medical conditions.

### Management of alcohol withdrawal

The approach to alcohol withdrawal is shown in Figure 2.

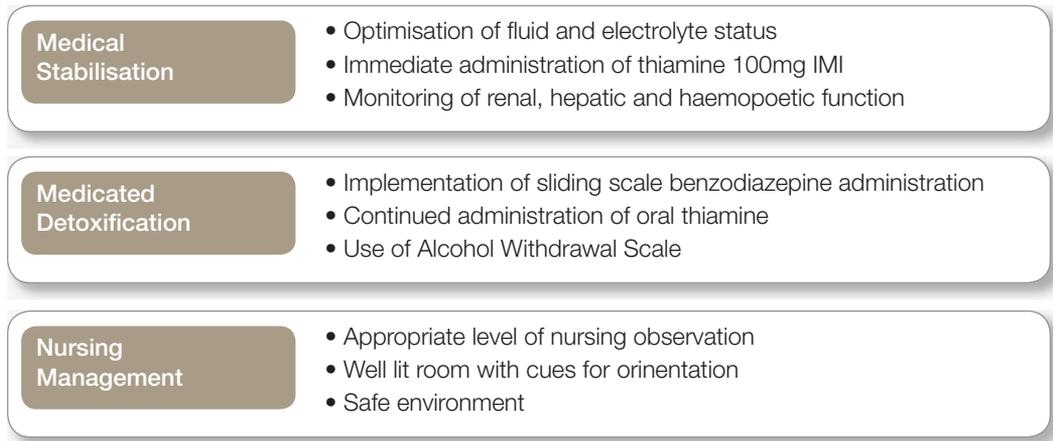


Figure 2 – The management of alcohol withdrawal

The general approach to the management of alcohol withdrawal is a coordinated management approach involving medical and nursing interventions. The patient must receive prompt administration of thiamine by the intramuscular route to prevent the onset of Korsakov's syndrome. As many patients may be inadvertently offered glucose containing fluids, there is a significant risk of haemorrhagic infarction of the mammillary bodies due to an accumulation of alpha-ketoglutarate (an intermediate step in the Krebs's cycle requiring thiamine as a co-factor). Parenteral thiamine is necessary as the gut absorption of thiamine is negligible in patients who drink excessively. This improves 24-48 hours after cessation of drinking so oral thiamine (100mg bid) can be introduced within 1-2 days. Electrolyte status must be stabilised, particularly given that hypokalaemia and hypomagnesaemia are risk factors for the development of alcohol withdrawal delirium.

The definitive management of alcohol withdrawal involves the administration of a benzodiazepine agent, dosed according to the level of symptomatic disturbance evident after the administration of the "Alcohol Withdrawal Scale" (AWS). Benzodiazepines and alcohol both activate the GABA receptor, so there is cross tolerance between the two. Some centres opt for a 'loading dose' regimen, usually 20mg of diazepam statim, followed by a phased reducing dose of diazepam over the ensuing 3-5 days. The sliding scale approach of the AWS provides the advantage of flexible dosing. Diazepam is the usual benzodiazepine used for such regimes, however lorazepam or oxazepam do not require hepatic metabolism and may be more appropriate to use with patients where there are concerns about hepatic insufficiency.

The safe nursing management of alcohol withdrawal is akin to the management of other forms of delirium and involves the provision of an environment that is safe for the patient and has obvious visual cues to orientate the patient, such as clocks and calendars.

### Post-Acute Management of Alcohol Misuse

Following the safe detoxification of the patient from alcohol, various management challenges emerge, including psychosocial, medical and psychiatric complications of alcohol misuse. This phase of intervention, usually referred to as "relapse prevention" usually involves the patient engaging in specialist Drug and Alcohol services. Some patients may continue to experience physical cravings for alcohol. The prescription of acamprosate sodium (333mg – 666mg tds) or naltrexone (50mg mane) may be recommended to alleviate such symptoms.

### Benzodiazepine Withdrawal Syndromes

The abuse of benzodiazepines is uncommon, however the withdrawal syndrome which emerges from abrupt discontinuation of benzodiazepines is quite symptomatically severe. The withdrawal syndrome is more rapidly evident and severe when the patient's drug of choice is a benzodiazepine with a short half-life, such as alprazolam or oxazepam. As benzodiazepines are either sourced from medical practitioners, or illicit sources, there is no distinct demographic pattern to describe patients at risk for benzodiazepine dependence. Benzodiazepine withdrawal syndromes may become evident in specialist drug and alcohol or psychiatric settings, but may also occur in medical

or surgical settings. A paradigmatic example of this is that of an elderly patient who has taken a benzodiazepine agent chronically as a nocturnal sedative, who is admitted to a medical or surgical unit in an emergency and the likelihood of benzodiazepine withdrawal is not considered. As there is a low index of suspicion of benzodiazepine use in such patients, such withdrawal syndromes are often missed.

Benzodiazepine withdrawal syndromes often emerge slowly, and are varied in either the severity or nature of their presentation (Figure 3).

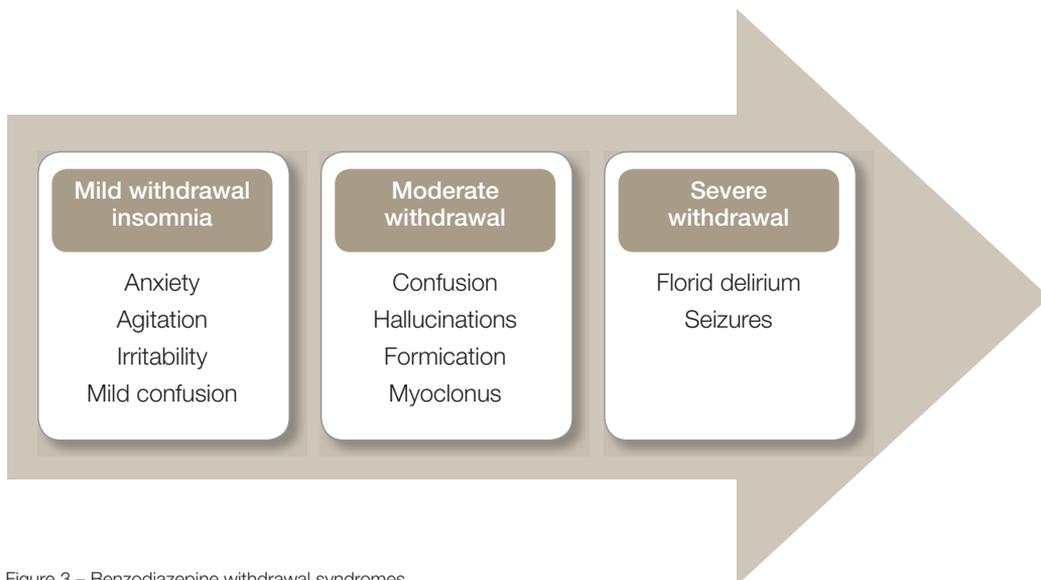


Figure 3 – Benzodiazepine withdrawal syndromes

The management of benzodiazepine withdrawal involves establishing the amount of benzodiazepines the patient uses, the conversion of this into an equivalent amount of diazepam, and the implementation of a graded withdrawal regime (Table 2).

Agent	t ½	Dose Equiv
<b>Diazepam</b>	<b>20-100</b>	<b>10</b>
Alprazolam	6-12	0.5
Bromazepam	10-20	5-6
Chlordiazepoxide	5-30	25
Clobazam	12-60	20
Clonazepam	18-50	0.5
Flunitrazepam	18-26	1
Lorazepam	10-20	1
Nitrazepam	15-38	10
Oxazepam	4-15	20
Temazepam	8-22	20
Triazolam	2	0.5

Table 2 – Dose equivalents of benzodiazepines.

Some centres recommend the patient be stabilized on a dose of diazepam equivalent to 50% of the patient's habitual use of benzodiazepines, with a graded reduction following on from this. As some accounts of benzodiazepine use can be unreliable, monitoring the patient for signs of benzodiazepine withdrawal or overdosing is good practice. If a patient described using 2-3mg of alprazolam per day, this would translate into a dose of 40-60mg per day of diazepam. Such a patient would be stabilized on a dose of 20-30mg diazepam daily.

The rate of subsequent reduction of benzodiazepine dose is controversial. Some inpatient detoxification centres offer rapid detoxifications over periods of 7-10 days, whereas others advocate conservative reductions of 10% of the dose of benzodiazepine per week over the subsequent 2-3 months. The choice of method is more related to patient and clinician preference, rather than specific evidence either way.

### LEARNING OBJECTIVES

- Describe the clinical features of opiate withdrawal syndromes
- Outline the pharmacological management of opiate withdrawal syndrome, including symptomatic treatment and opiate substitution
- Outline methadone and buprenorphine opiate substitution treatment

## The management of opiate withdrawal and dependence

### Introduction

Illicit opiates such as heroin are the third most common illicit substance used worldwide. In Australia, approximately 0.5% of the population has used illicit opiates in the past year (1). Of those people who use opiates, one in four may become dependent, and this can occur after 6 – 8 weeks of regular use. Illicit opiate use and dependence is associated with significant health and social problems including deaths from accidental overdose, transmissible diseases such as hepatitis C and HIV, legal problems and social disadvantage. Illicit opiate users may use heroin, diverted methadone, and buprenorphine or prescribed opiates (1). Where opiates are not available, benzodiazepines, alcohol or other substances may be used to control withdrawal symptoms.

Chief actions
Analgesia
Sedation
Respiratory depression
Euphoria
Other actions
Decreased blood pressure
Constriction of the pupils
Decreased gastric emptying
Reduced gastrointestinal motility
Elevated pyloric sphincter tone
Elevated tone of sphincter of oddi (can cause biliary spasm)
Endocrine actions including:
Reduced follicle stimulating hormone / luteinising hormone / testosterone
Elevated prolactin
Reduced adrenocorticotrophic hormone
Elevated antidiuretic hormone
Suppressed cough
Side effects
Sleep disturbances
Nausea and vomiting
Constipation
Dry mouth
Sweating
Vasodilation and itching
Menstrual irregularities in women
Gynaecomastia in men
Sexual dysfunction
Fluid retention and weight gain

Table 1: Effects of opioids

### Patterns of use

Opiate use in the community varies from sporadic use to severe dependence states. Where the individual does not meet the criteria for opiate dependence but as a result of ongoing use recurrently experiences social or legal problems, fails to meet obligations or uses in hazardous situation, then a diagnosis of illicit opioid harmful use is made. Opiate dependence is diagnosed when at least three of the following criteria are met, Impaired control over use, craving or compulsion to use, salience, tolerance, withdrawal or use to prevent withdrawal and persistent use despite harm. Opiate use and dependence are associated with a number of complications (Table 2).

### Treatment options

There are a range of psychosocial and pharmacological treatments available for the management of harmful opioid use and dependence. Psychosocial treatments include therapeutic communities, self help groups such as narcotics anonymous, and counselling and support services. Pharmacological treatments include withdrawal management, opiate substitution therapy and naltrexone. Case management is strongly recommended, particularly where there are multiple professionals involved in care.

Acute complications		
<b>Overdose</b>	Respiratory depression resulting in reduced SaO <sub>2</sub> and potentially death Rhabdomyolysis – from pressure due to prolonged unconsciousness	
<b>QTc Prolongation</b>	methadone, especially at high doses Risk increased with concurrent use of other medications causing QTc prolongation	
<b>From injecting</b>	Contaminants / adulterants infection – Non sterile technique  Sharing equipment Vascular complications  Sexually transmitted infections	Variable potency => overdose risk Allergic reaction to contaminants <u>Local infections</u> Abscess, cellulitis, necrotising fasciitis <u>embolic infections</u> bacterial endocarditis, metastatic abscesses, osteomyelitis, septic arthritis <u>Systemic infections</u> Septicaemia and disseminated infection risk of BBV including Hepatitis B, C and HIV Vascular damage from injecting distal ischaemia due to Arterial injection strokes and emboli aneurysms (such as mycotic aneurysm) pulmonary emboli / infarction through unprotected sex, or sex work as a means ongoing use
Chronic complications		
<b>Chronic infection</b>	Hepatitis B and C  HIV	Risk of cirrhosis and its complications risk of transmission with unsafe practices Immunodeficiency with progression of illness Risk of transmission
<b>Dental</b>	Xerostomia results in bacterial proliferation and dental decay	
<b>Constipation</b>	Constipation is a side effect of opiate use and dependence, including opiates used in maintenance treatment	
Social complications		
<b>Vulnerability</b>	Particularly whilst intoxicated	
<b>Violence</b>	Potentially through criminal association obtaining illicit substances	
<b>Legal</b>	Legal problems as a result of drug possession or from criminal activity to finance substance use. Periods of imprisonment are common.	
<b>Relationships</b>	Relationship difficulties due to substance use associated legal problems potential child neglect as a consequence of substance use	
<b>Margininalisation</b>	Stigma and marginalisation associated with illicit substance use	
Psychiatric complications		
<b>Depression &amp; anxiety</b>	Mental disorders due to the direct effect of a substance and through social adversity and exposure to trauma	

Table 2: Complications associated with opiate use

### Features of Opiate withdrawal

Opiate withdrawal syndrome varies with the quantity and duration of opiate use, and the health of the individual. Withdrawal may resemble flu like illness, and uncomplicated withdrawal is not life threatening. The severity of withdrawal symptoms varies in accordance with the quantity and duration of opiate use and the health of the individual. The onset of withdrawal varies according to the substance being used. Heroin is a relatively short-acting drug so withdrawal occurs within hours of last use. Withdrawal from a long-acting opioid such as methadone commences later than that for heroin, has a lower peak severity but is more prolonged. Withdrawal from buprenorphine is generally milder than either methadone or heroin because of slow dissociation from the mu ( $\mu$ ) receptor. Following acute withdrawal, a protracted less severe withdrawal may last months, this is characterised by low-grade symptoms of physical and psychological discomfort. Patients in institutional care such as hospitals or prisons will not always reveal their use of opioids and so may undergo unplanned opioid withdrawal. Possible indicators may include objective signs of recent use such as 'track marks' and repeated requests for opiate analgesia often in excess of what would be expected for a given clinical circumstance.

Drug	Onset	Peak withdrawal	Duration
Heroin	6 – 24 hours	24 – 48 hours	5 – 10 days
Methadone	36 – 48 hours	3 – 4 days	3 – 6 weeks
Buprenorphine	3 – 5 days	5 days	Several weeks

Table 3: Onset and duration of opiate withdrawal symptoms

Physical symptoms
Vomiting
Diarrhoea
Anorexia and nausea
Abdominal pain
Hot and cold flushes
Bone, joint and muscle pain
Abdominal Cramps
Muscle twitching (particularly restless legs while lying down)
Rhinorrhoea, lacrimation
Physical signs
Yawning
Rhinorrhoea, Lacrimation
Dilated pupils
Perspiration
Piloerection ('cold turkey')
Fever (low grade)
Tachycardia, hypotension
Psychiatric symptoms and signs
Intense craving for opioids +/- drug seeking behaviour
Restlessness, agitation
Irritability, depression, anxiety
Insomnia and disturbed sleep

Table 4: Signs and symptoms of opiate withdrawal

### Management of opiate withdrawal

Hospital admission is not normally indicated for opiate withdrawal unless there is severe vomiting, intercurrent illness, pregnancy or concurrent dependence on alcohol or benzodiazepines.

A comprehensive assessment including a consumption history for each substance, psychiatric, medical and social assessment will help define the risks to the patient, their dependents and any potential barriers to successful withdrawal. An empathic and non-judgmental approach coupled with support and encouragement are important aspects of the treatment environment. Acknowledgment of an individual's knowledge with regard to drug use, withdrawal and treatment is important. Misinformation and misunderstanding of withdrawal, treatments options and health provider's responses should be sensitively elicited and responded to with objective information. This can assist with development of short and long-term goals of treatment. Identifying complications of substance use should be done, including investigations for blood born pathogens and other medical complications of use.

During withdrawal regular monitoring should occur using an appropriate withdrawal scale, based on observations, subjective symptoms and objective signs. Available scales include The Clinical Opiate Withdrawal Scale (COWS) or The Subjective Opiate Withdrawal Scale (SOWS). Regular re-evaluation of the patient is important, particularly if the patient is not responding well. This can prevent missing a co-occurring medical conditions or withdrawal state. Useful adjuncts during the withdrawal include general supportive measures, adequate hydration and nutrition, rest and reassurance.

The regulatory context of the treatment of addiction is important to note. In Australia, it is not legal to prescribe Schedule 8 drugs to treat addiction to anyone who is a known addict without an individual authority to prescribe from a state health department. In hospital settings, medical practitioners may use methadone or buprenorphine to assist in the management of hospitalised opioid dependent individuals. Outside of the hospital setting, only medical practitioners authorised to deliver treatment with buprenorphine or methadone for the management of opioid dependence may deliver this treatment.

Pharmacotherapy for opiate withdrawal can include either short-term withdrawal by opiate substitution or symptomatic treatment. Some individuals may elect to begin maintenance pharmacotherapy rather than withdraw (2,4). The principal treatment option for managing opioid withdrawal is buprenorphine. Caution should be taken with concomitant use of other sedating medications due to the risk of respiratory depression. Buprenorphine is a partial agonist and strongly binds to opioid receptors. These pharmacological properties mean it interferes with the effectiveness of other opioids prescribed for analgesia. Opiate withdrawal can also be managed by substitution with small to moderate doses of methadone. This strategy tends to provide less rapid relief of withdrawal symptoms because doses cannot be increased quickly due to the risk of accumulation and opiate toxicity (4).

If someone who has recently used heroin (in the previous 12 hours) or methadone (in the previous 48 hours), treatment with buprenorphine can precipitate withdrawal. As such treatment should not begin until COWS score of at least 8, indicating mid point of the scale, or a SOWS score of 16–25 representing mild to moderate withdrawal (4). An initial dose of 4mg or less minimises the risk of precipitated withdrawal, and a follow up dose after 4 hours is required based on withdrawal phenomena (4). The recommended treatment duration for heroin withdrawal using buprenorphine is 4 – 8 days, with daily review and dose adjustments during the first few days. An example regime for withdrawal can be seen below in table 5. Because of street diversion, buprenorphine is also available in combination with naloxone. When used intravenously the naloxone precipitates opiate withdrawal in dependent users, thereby deterring intravenous abuse. A newer sublingual films has recently become available, which dissolves faster and adheres to the oral mucosa. This creates additional barriers to diversion for illicit use (4). Naltrexone-assisted opioid withdrawal is a valuable treatment option for some patients, but is not recommended in standard clinical settings (4).

Day	Buprenorphine dose (and suggested range)
1	6mg (4 – 8 mg) usually 2mg test dose, then further dose in no precipitated withdrawal
2	8mg (4 – 12mg)
3	10mg (4 – 16mg)
4	8mg (2 – 12mg)
5	4mg (0-8mg)
6	0mg (0 – 4mg)
7	0mg ((0 – 2mg)
8	0mg (0 – 1 mg)

Table 5 : example buprenorphine regime

Symptomatic treatment and supportive care is often sufficient in treating mild withdrawal. Symptoms can be controlled using non opiate medication as seen below in Table 6

Symptom	Medication
Anxiety, agitation, insomnia	Diazepam 5 – 10mg PRN QID Sedating antihistamine or temazepam for insomnia
Nausea / vomiting	Metoclopramide 10mg TDS or PRN orally / IMI <b>OR</b> Prochlorperazine 5 mg, 4–6 hourly PRN
Abdominal cramps	Hyoscine butylbromide 20mg PRN QID orally or IMI
Diarrhoea	Loperamide 2mg initially, then 1 tablet after each unformed stool, upto 8 tabs per day
Muscle aches / pain	Paracetamol 1g PRN QID (maximum 4g mg in 24 hours) <b>OR</b> Ibuprofen 400 mg PRN QID (if no history of peptic ulcer or gastritis)
Sweating, agitation	Clonidine 75 µg every 6 hours – Take baseline blood pressure & heart rate before first dose. – Do not use clonidine if: 1. hypotensive (blood pressure < systolic 90 or diastolic 50 mmHg) 2. bradycardic (heart rate < 50 per minute) 3. clinical evidence of impaired circulation. Initial test dose: 4. 75 µg test dose 5. monitor for blood pressure, lying and standing after half an hour.

Table 6 : symptomatic treatment of opiate withdrawal (4)

Withdrawal from opiates presents an opportunity for lasting abstinence. Patients should be informed of post withdrawal management and support options, and linked with continuing care. Management

options include abstinence, medication supported abstinence (naltrexone) and opiate substitution therapy. Support services including Narcotics Anonymous, outpatient programs, counselling and residential services can provide ongoing treatment and support.

### **Opiate treatment programs – methadone and buprenorphine maintenance treatment**

Once established, opioid dependence tends to be a chronic and relapsing condition. Many opioid users who attempt withdrawal will relapse back into use. Extensive research demonstrates the effectiveness of methadone and buprenorphine maintenance treatment in the management of opioid dependence. These treatments are effective in reducing heroin use and associated crime, reducing the risk of death by overdose, reducing the spread of blood born viruses associated with injecting opioid use. They also enable individuals to resume their social and vocational obligations and improve the health, wellbeing, function of individuals and families. Treatment for opiate dependence is provided through specialist public and private outpatient clinics, General practitioners, community pharmacies, prisons, and through hospitals in regional areas. Prescribers include medical practitioners and nurse practitioners.

There are a number of legal requirements for commencing on opioid substitution therapy. These include but are not limited to, documented proof of identity of the patient and an Authority to prescribe methadone or buprenorphine to the patient from the Pharmaceutical Services branch of NSW Health. All patients should commence treatment in a well supervised setting, but once stabilised can potentially be dosed through pharmacies.

### **Methadone**

Methadone is a synthetic opioid agonist with a long half-life, making it a useful agent for the treatment of opioid dependence. With repeated dosing the half-life increases, contributing to rising blood levels during the first week of daily dosing. This phenomenon necessitates clinical vigilance particularly during the first 14 days of treatment, as individuals are at risk of opioid toxicity and death, particularly if other sedatives are being used concurrently. Once stabilised, the long half-life and minimal fluctuations in serum concentrations between daily doses prevent the onset of significant withdrawal. However some individuals experience withdrawal symptoms before their next dose is due. If this is not prevented by dose increases or split daily dosing then buprenorphine may be preferable.

Most people who have used heroin will experience few side effects from methadone. Typical side effects include effects on cognitive ability and attention, constipation, sexual dysfunction, weight gain, sweating, poor sleep and dental problems. Methadone is extremely toxic to non-tolerant individuals, especially children. Take away doses require adherences to precautions around the storage of doses. Methadone is associated with prolonged QTc interval, particularly at higher doses (>100 mg/day). This effect should be taken into consideration, particular interest in those patients with concurrent cardiac disease and patients who are prescribed other drugs that might prolong the QTc interval, such as antipsychotics.

Methadone is primarily broken down in the liver via the cytochrome P450 enzyme system. Significant liver disease or impairment can affect its clearance, increasing the risk of accumulation, toxicity and death. In patients with severe respiratory disease, doses should be monitored closely to avoid significant respiratory depression and respiratory failure. There are a number of important drug interactions between methadone and other drugs that have been associated with toxicity and death. These are detailed in Table 7.

The starting dose of methadone depends on the severity of dependence, level of tolerance, time since last opioid use and whether there is comorbid benzodiazepine or alcohol use. Typical initial doses are in the range of 20 – 40mg per day, a dose of 20mg for a 70kg person can be presumed to be safe. If possible, patients should be observed for 3–4 hours after the first dose for signs of toxicity or withdrawal. Doses are typically adjusted every fourth dose by 5mg, or up to 10mg when on higher maintenance doses. Daily methadone doses of >60 mg or more are associated with better treatment outcomes. If a patient is to be transferred to buprenorphine, methadone should be reduced to 40mg or less per day, and should have been on this dose for at least one week. Buprenorphine should then not be given until at least 24 hours after the last methadone dose.

<b>Other sedatives</b>	Sedation produced by opioids, alcohol, benzodiazepines, tricyclic antidepressants, major tranquillisers and sedating antihistamines is additive with the sedation associated with methadone. Deaths have been reported.
<b>Opioid antagonists</b>	The effects of methadone are reversed or inhibited by naltrexone and naloxone. This can precipitate acute withdrawal
<b>Buprenorphine</b>	Those taking 40 mg or more of daily methadone are likely to experience precipitated withdrawal if given buprenorphine
<b>Opioid agonists</b>	Effects are additive to the pharmacodynamic effects of methadone and may cause overdose and death
<b>Hepatic enzyme inhibitors and inducers</b>	Methadone is metabolised by the cytochrome P450 3A4 enzyme system. Cytochrome P450 inducers accelerate the metabolism of methadone and precipitate withdrawal; inhibitors of cytochrome P450 slow the metabolism of methadone and can produce toxicity and overdose
<b>Highly active antiretroviral therapy</b>	Some drugs used in the treatment of HIV alter methadone pharmacokinetics

Table 7: Methadone drug interactions (5)

	Methadone	Buprenorphine
<b>Onset of effects</b>	30 minutes	30–60 minutes
<b>Peak effects</b>	About 3 hours	about 1–4 hours
<b>Half-life</b>	14–58 hours	20–72 hours
	Blood levels rise during the first Week of daily dosing at a stable dose	
<b>Stabilisation of levels</b>	5–10 days	7–10 days
<b>Withdrawal</b>	Begin 36–48 hours after last dose Peak at 5–7 days Most signs of withdrawal not observed after 21 days	begin within 3–5 days of last dose can last for several weeks Withdrawal typically milder than that for other opioids due to slow dissociation from receptors

Table 8: Pharmacokinetics of methadone and buprenorphine

### Buprenorphine

Buprenorphine is a partial opioid agonist with less euphoric, sedating and respiratory depression effects than pure opioid agonists. These effects tend to plateau at relatively low doses (4 – 8mg) making it safer in overdose than other opioid drugs. It is effective in diminish cravings for opioids and in prevent or alleviate opioid withdrawal in people with opioid dependence. Its strong affinity for opioid receptors can reduce the effect of opioid agonists by preventing them from occupying receptors. This interaction can precipitate opioid withdrawal in dependent persons who have recently used methadone or heroin. Buprenorphine has poor oral bioavailability because of extensive first pass metabolism in the small intestine and the liver. It has better sublingual bioavailability and so is available in tablets for sublingual administration and in combination with naloxone as sublingual tablets and sublingual film. The combination with naloxone, an opioid antagonist, is a strategy to reduce its diversion for injection. Oral naloxone has no effect, whereas injected naloxone reverses the effect of opioids and precipitates withdrawal in dependent individuals.

Buprenorphine is metabolised by the liver via the cytochrome P450 enzyme system (CYP 3A4), so should be used with caution in individuals with hepatic disease. In patients with severe respiratory disease, doses should be monitored closely to avoid significant respiratory depression and respiratory failure. Buprenorphine has a number of relatively common side effects. Which typically peak at the start of treatment. Like other opioids it has effects on cognition and attention and can cause constipation, sexual dysfunction and increased sweating. Other side effects include cold or flu-like symptoms, headaches, sleeping difficulties, nausea, and mood swings.

<b>Other sedatives</b>	The sedation produced by opioids, alcohol, benzodiazepines, tricyclic antidepressants, major tranquillisers and sedating antihistamines is additive with the sedation associated with Buprenorphine. Deaths have been reported.
<b>Opioid antagonists</b>	Buprenorphine has a higher affinity for opioid receptors than either naltrexone or naloxone. Very high doses of naloxone are required to reverse a buprenorphine overdose
<b>Opioid agonists</b>	Buprenorphine can precipitate withdrawal if taken by opioid dependent individuals while other opioids are active. It also interfere with the analgesic effect produced by other opioids
<b>Hepatic enzyme inhibitors &amp; inducers</b>	Buprenorphine is metabolised by the cytochrome P450 3A4 enzyme system. Drugs which inhibit or induce its activity may affect buprenorphine levels.

Table 9: Buprenorphine drug interactions

Because of the risk of precipitated withdrawal, Buprenorphine should not be started until 8-12 hours after last heroin use, or 24-36 hours after last dose of methadone. An 8mg initial dose is generally well tolerated, however due to the risk of precipitated withdrawal a test dose of 2-4 mg with the option of a further dose up to 8mg on day one is commonly used. Doses are usually increased over the following two days to reach a dose of 16mg by day 3. Higher induction schedules are associated with toxicity or side effects. In general doses can be increased by 2-8mg daily, to a maximum dose of 32 mg.

	Methadone	Buprenorphine
<b>Pharmacology</b>	<ul style="list-style-type: none"> <li>• Long half-life</li> <li>• full agonist</li> <li>• Doses exceeding individual's tolerance can cause toxicity and death</li> </ul>	<ul style="list-style-type: none"> <li>• Long half-life</li> <li>• partial agonist</li> <li>• High affinity &amp; slow dissociation from receptors</li> <li>• Plateau on opioid effects despite increasing doses</li> </ul>
<b>Induction</b>	<ul style="list-style-type: none"> <li>• Doses &gt; 30 mg can be fatal in the opioid-naïve</li> <li>• Doses should be withheld if patient appears intoxicated or sedated (risk of fatal respiratory depression)</li> <li>• Progressive increase in plasma levels during first week of treatment on a stable dose</li> <li>• Regular (daily) monitoring for toxicity</li> <li>• First doses in the range 20-40 mg.</li> <li>• Doses should be increased gradually</li> <li>• Dose at the end of the first week 40 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of Precipitated withdrawal: – start once there is evidence of withdrawal. (8-12 hours after last heroin, &gt; 24 hours after methadone)</li> <li>• High dose rapid induction safe &amp; effective. Start at 8 mg and aim for 16 mg by Day 3</li> <li>• Rapid induction can produce side effects</li> <li>• Less risk of respiratory depression than with full agonists</li> <li>• Doses should be withheld if patient appears intoxicated or sedated (risk of fatal respiratory depression)</li> </ul>
<b>Maintenance</b>	<ul style="list-style-type: none"> <li>• To achieve adequate suppression of heroin use, increase dose in weekly increments of 10 mg to maintenance dose</li> <li>• Typical maintenance dose 60-100 mg/day</li> <li>• During first month of treatment, review patient weekly</li> <li>• Urine testing is useful to supplement self-reported drug use</li> </ul>	<ul style="list-style-type: none"> <li>• Doses <math>\geq</math> 12 mg/day usually required for optimal maintenance</li> <li>• Review weekly for first month</li> <li>• Urine testing is useful to supplement self-reported drug use</li> <li>• After 7-14 days, if responding, consider trial of alternate daily dosing</li> <li>• If erratic attendance, or ongoing drug use, consider switching to methadone</li> </ul>

Table 10: Induction and stabilisation: buprenorphine and methadone compared (2)

### Naltrexone

Oral naltrexone, an opioid antagonist, is considered an appropriate treatment option in detoxified formerly opioid-dependent people with adequate supervision and who have high motivation to remain abstinent. Naltrexone is available as a 50mg tablet. Subcutaneous implants and intramuscular depots have been developed but are not licenced in Australia. Patients taking naltrexone rapidly lose tolerance to opioids and so should be warned of the risk of overdose if they relapse to use. If transferring a patient from naltrexone to opioid treatment methadone or buprenorphine should not be given until at least 72 hours after the last dose of naltrexone. Starting doses should be no greater than 20 mg of methadone or 4 mg of buprenorphine.

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#### Further Reading

1. Noeline Latt, et al (2009). *Addiction Medicine*. Oxford: Oxford University Press.
2. Mental Health and Drug & Alcohol Office, NSW Department of Health : NSW Opioid Treatment Program Clinical guidelines for methadone and buprenorphine treatment, [internet,last updated 2006; cited 10.08.2012] Available from: [http://www.health.nsw.gov.au/policies/gl/2006/pdf/GL2006\\_019.pdf](http://www.health.nsw.gov.au/policies/gl/2006/pdf/GL2006_019.pdf)
3. American Psychiatric Association, (2000). *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision). Washington, DC.
4. Mental Health and Drug & Alcohol Office, NSW Department of Health: NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines, [internet,last updated 2008, cited 10.08.2012] Available from: [www.health.nsw.gov.au/policies/gl/2008/pdf/gl2008\\_011.pdf](http://www.health.nsw.gov.au/policies/gl/2008/pdf/gl2008_011.pdf)
5. Lingford-Hughes, A.R., Welch, S., Peters, L., Nutt, D. J., et al (2012). BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *J Psychopharmacol*, July 2012 26: 899-952.

#### LEARNING OBJECTIVES

- Outline the features and epidemiology of delirium
- Describe the causes and investigation of delirium
- Implement a management plan for delirium

## Recognition and management of delirium

### Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), the diagnostic criteria for delirium are<sup>70</sup>:

- Disturbance of consciousness with reduced ability to focus, sustain, or shift attention;
- Change in cognition or development of a perceptual disturbance that is not better accounted for by dementia;
- Acute onset with a tendency for the condition to fluctuate over the course of the day;
- Evidence that the disturbance is caused by the direct physiological consequences of a general medical condition or a substance.

**Alternative terms include:** acute confusional state, acute brain syndrome, toxic psychosis, acute brain failure, postoperative psychosis.

### Epidemiology of delirium

Studies estimate that between 10-31% of medically ill patients in hospital have features of delirium<sup>71</sup>. This rate may be higher in certain patient groups such as those in Intensive Care Units and in patients following cardiac surgery. In the elderly the rate may be as high as 40%<sup>72</sup>. However, the

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<sup>70</sup>. American Psychiatric Association: Diagnostic and statistical manual of mental disorders, (DSM-IV), 4th Ed, Washington, DC, 1994, *American Psychiatric Association*.

<sup>71</sup>. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age and Ageing*. 2006;35:350-364.

<sup>72</sup>. Lipowski ZJ. Delirium (acute confusional states). *JAMA*. 1987;258:1789-1792.

condition is often missed. In one study delirium was missed in up to 67% of cases by physicians<sup>73</sup>. The risk factors for delirium<sup>74</sup> are shown in Table 1.

1. Advancing age
2. Cognitive impairment
3. Dehydration
4. Alcohol abuse
5. Significant medical illnesses: e.g. diabetes, cancer
6. Vision impairment
7. Malnutrition
8. Polypharmacy

Table 1. The risk factors for delirium

### Pathophysiology

Acetylcholine deficiency and dopamine excess are the neurotransmitter abnormalities most commonly implicated in delirium.

Almost any illness can contribute to the development of delirium. The most likely cause(s) in an individual patient will depend on the patient's age, medical history and on the clinical setting (for example, on a surgical ward it will be important to search for dehydration, electrolyte disturbance and to review post-operative analgesia). Even if a potential medical cause has been found, it is important to pursue other investigations as the aetiology of delirium is commonly multi-factorial.

The medical illnesses commonly associated with the onset of delirium are shown in Table 2<sup>75</sup>.

### Clinical Features of Delirium

When asked to review a patient on the medical wards it is important to consider delirium as a possible differential diagnosis regardless of the nature of the referral. Anxiety, depressed mood and apparent psychomotor retardation, psychotic symptoms as well as aggression and agitation may all be presenting features of delirium.

<sup>73</sup> Rockwood K, Cosway S, Stolee P, et al. Increasing the recognition of delirium in elderly patients. *Journal American Geriatric Society*. 1994;42:252-256.

<sup>74</sup> Weber JB, Coverdale JH, Kunik ME. Delirium: current trends in prevention and treatment. *Internal Medicine Journal*. 2004;34(3):115-121.

<sup>75</sup> Taken from:

° Cassem N, Murray GB, Lafayette JM, Stern TA. *Massachusetts General Hospital Handbook of General Hospital Psychiatry* fifth Edition, Philadelphia, 2004, Mosby.

– American Psychiatric Association. Practice Guidelines for the treatment of patients with delirium. *American Journal Psychiatry*. 1999;156(suppl 5):1-20.

### Central Nervous System Disease

- Vascular disease
- Infections – encephalitis, meningitis
- Epilepsy/postictal states
- Neoplasms
- Trauma

### Systemic Diseases

- Cardiovascular – cardiac failure, myocardial infarction
- Respiratory – hypoxia, hypercapnia
- Hepatic – encephalopathy
- Renal – acute/chronic renal failure
- Endocrine (hypo-or hyper-function) – pituitary, adrenal, pancreas (hypo/hyperglycaemia), parathyroid, thyroid
- Metabolic – dehydration, vitamin deficiencies (e.g. thiamine), electrolyte disturbances (Na, K, Ca, Mg, PO<sub>4</sub>), acidosis/alkalosis, heavy metals, malnutrition, anaemia
- Infection/Sepsis
- Neoplastic disease
- Autoimmune Diseases – vasculitis, SLE

### Substance-Induced (intoxication or withdrawal)

Prescribed medications:

- benzodiazepines
- anaesthetic agents
- those with anticholinergic effects (e.g. tricyclic antidepressants)
- opioids
- corticosteroids

Recreational Drugs/Alcohol

Table 2 – Medical Disorders Associated with the onset of delirium

A useful first step is to carefully read through the patient's medical file. Important information can be gathered regarding current and past medical illnesses and drug and alcohol history. The nursing notes are a particularly useful resource. These entries often give important clues that a patient may be confused or disorientated. Pay close attention to night-shift entries as night is a time when the symptoms of delirium may be most florid. A scan of past medical records may reveal previous episodes of delirium or a history of cognitive impairment. Next review the observation and medication charts. The medication list may suggest an aetiological cause but also consider medications that may have been missed (e.g. Does the patient normally take sleeping tablets? Have these been charted?). Collateral history from family, friends and/or general practitioner is also important. Occasionally, a prodromal phase may be evident characterised by vivid dreams, restlessness, distractibility, irritability and tearfulness. This phase may occur 1-3 days prior to the onset of the full syndrome<sup>76</sup>. Delirium tends to have an acute onset over hours to days and a fluctuating course. It may be useful to see patients at different times of the day to detect this. The clinical features of delirium are shown in Table 3.

<sup>76</sup> Trepacz P, Breitbart W, Franklin J, Levenson J, Martini DR, Wang P. Practice guidelines for the treatment of patients with delirium. *American Psychiatric Association*.

- 1) **Consciousness:** clouding (reduced awareness of surroundings)
- 2) **Cognition:** generalised impairment that affects orientation (time>place>person), attention (poorly performed digit span), memory (recent memory most affected), planning and organisational skills
- 3) **Behaviour:** disturbance of sleep-wake cycle, agitation or psychomotor retardation
- 4) **Mood/Affect:** dysphoria, irritability, anxiety, euphoria, apathy
- 5) **Perceptual disturbance:** misinterpretations, illusions or hallucinations (visual> auditory) often with secondary delusional beliefs (delusions often persecutory in nature and poorly systematised)
- 6) **Clinical features associated with the underlying aetiology:** (e.g. jaundice, hepatic fetor and asterixis from hepatic encephalopathy)

Table 3 – Clinical Features of Delirium

Some authors divide delirium into two groups – hypoactive and hyperactive<sup>77</sup>:

- *Hypoactive Delirium:* decreased activity, decreased alertness, somnolence, lethargy, apathy, EEG slowing, e.g. hepatic encephalopathy
- *Hyperactive Delirium:* increased activity and alertness, hypervigilance, fast or loud speech, irritability, wandering, EEG may be normal, possibly more likely to have hallucinations and delusions, e.g. alcohol withdrawal, anticholinergic toxicity

There are rating scales available for screening (e.g. Clinical Assessment of Confusion-A<sup>78</sup>), diagnosis (e.g. Confusion Assessment Method<sup>79</sup>) and severity (e.g. Delirium Rating Scale<sup>80</sup>).

### Differential Diagnoses of Delirium

*Dementia:* will have a more chronic, insidious course; fluctuations in cognition are less marked; attention less affected; consciousness is clear until the late stages; psychotic symptoms are less common. However, dementia will make individual patients more susceptible to delirium and delirium may be superimposed onto dementia – consider if acute deterioration and fluctuating symptoms. Collateral history may be needed to clarify the patient's baseline cognition. Consider Lewy Body Dementia that may be associated with a fluctuating cognition and visual hallucinations.

*Depression:* hypoactive delirium may be misdiagnosed as depression. Depression will be associated with diurnal variation, a more subacute onset but with no clouding of consciousness or disorientation.

*Manic episode:* the agitated and irritable delirious patient may appear manic. In mania there will be more goal directed behaviour and less cognitive impairment.

*Psychotic illness:* hallucinations and delusions more constant and systematised than in delirium, and there is usually no clouding of consciousness or disorientation.

*Substance intoxication or withdrawal:* the patient who is affected by a substance may be somnolent or agitated but will not be considered delirious unless the cognitive impairment is out of proportion to what would be normally expected from the implicated substance.

<sup>77</sup> a. Lipowski ZJ. Delirium (acute confusional states). *JAMA*. 1987;258:1789-1792.

b. Ross CA, Peyser CE, Shapiro I. Delirium: phenomenologic and etiologic subtypes. *Int Psychogeriatr*. 1991;3:135-147.

c. Liptzin B, Levkoff SE. An empirical study of delirium subtypes. *British Journal Psychiatry*. 1992;161:843-845.

<sup>78</sup> Vermeersch PE. The clinical assessment of Confusion- A. *Appl Nurs Res*. 1990;3:128-133.

<sup>79</sup> Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method, a new method for the detection of delirium. *Ann Intern Med*. 1990;113:941-948.

<sup>80</sup> Trezepacz P, Baker R, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Res*. 1988;23:89-97.

### *Investigations*

The investigations performed will depend on the clinical situation (Table 4).

1. Bloods – UEC, Ca/Mg/P04, LFT, FBC, glucose, TFT, blood cultures, ESR, drug levels
2. Urine – urinalysis, MSU
3. ECG
4. EEG
5. Cerebral CT scan/MRI
6. CXR
7. ABG/ pulse oximetry
8. Other – LP/CSF, B12/folate

Table 3 – Investigation of Delirium

### **Management of Delirium**

#### *Risk Management*

An important aim of treatment is to maintain the safety of the patient, other patients and staff. Patients' with delirium are at risk of suicide, falls, wandering and medical complications. They may be aggressive and try to defend themselves in the face of perceived persecution.

Consideration should be given for the patient to be treated in a single room with 1:1 nursing care. 'Chemical restraint' may be needed (see below) to reduce behavioural disturbance. Physical restraints (posey jackets, wrist restraints) are usually used as a last resort. Procedures for their application and indications for their use will depend on local policies. It should be remembered that the least restrictive option should be used for the shortest amount of time. Ensure adequate hydration, food intake and toileting. Monitor for the development of pressure areas, venous stasis and pneumonia. Access to open windows, balconies, stairwells and other potential environmental dangers should be prevented.

#### *Medicolegal Considerations*

Patients with delirium are likely to have impaired capacity to make decisions about their medical treatment. As delirium is a medical emergency most patients may be detained in hospital and provided with medical treatment under 'Duty of Care'. An application to the Guardianship Board may also be considered.

#### *Environmental Changes/ Reorientation*

Environmental changes that may help the delirious patient feel less distressed and minimise behavioural disturbance include: having a family member or close friend present, or place photos of loved ones in their room; trying to maintain consistency of staff; providing a room close to the nursing station; having easily sighted clocks and calendars and encouraging staff to repeatedly reorientate the patient; the use of a single room, if possible, to avoid over-stimulation but avoiding too little stimulation by the use of soft lighting and gentle background music. Making sure the patient has glasses or hearing aids, if these are required, will help reduce misperceptions. Education and reassurance to the family and to the patient, if possible, is also important.

#### *Pharmacological treatment*

The evidence for the use of psychotropic medications in the setting of delirium is limited. Consideration for medication should be given when the patient is agitated, distressed, sleepless or has psychotic symptoms. In patients who have hypoactive delirium, there is some evidence that medications may reduce the duration of the delirium and decrease distress. Like with all decisions regarding treatment the benefits must be weighed against the risks. Psychotropic medication may result in falls, may impair the patients ability to understand and comply with treatment, and sedative medication may worsen cognitive impairment.

The most studied medication for the treatment of delirium is haloperidol. Haloperidol may be used in doses from 0.5mg to 10mg and has the benefit of oral and parental administration. The dose and frequency of administration will depend on the clinical situation. It has few anticholinergic or hypotensive effects. It may result in a prolonged QT interval on ECG and, therefore, potentially result in an increased risk of Torsades de Pointes. The patient must also be monitored for extrapyramidal side effects but, in the setting of delirium treated with haloperidol, the incidence of these effects is low<sup>81</sup>. Olanzapine (up to 20mg/day), risperidone (up to 4mg/day), quetiapine (~200mg/day) and ziprasidone have also been used in the treatment of delirium. Olanzapine may be better tolerated than haloperidol and can be given intramuscularly. The evidence for these medications is limited. It has been suggested that antipsychotic medication be continued for a further 7-10 days following resolution of symptoms<sup>82</sup>. Benzodiazepines may worsen confusion or cause disinhibition in the elderly, or in patients with pre-existing organic brain syndromes, and should be avoided in most cases. The exceptions to this rule are the setting of alcohol or benzodiazepine withdrawal and postictal delirium.

#### *Identify and Treat the Underlying Cause(s)*

This will depend upon the clinical situation.

#### **Prognosis of Delirium**

There may be a rapid improvement in symptoms once the underlying cause has been found and adequately treated. Delirium often subsides over 10-12 days<sup>83(1)</sup> but maybe more prolonged in the elderly (up to 81 days<sup>84</sup>).

Delirium has been associated with:<sup>85, 86</sup>

- Prolonged hospitalisation
- High frequency of complications e.g. falls, infections, pressure sores
- Increased need for care in institutions
- Increased risk of death

The mortality rate for patients who have had delirium is between 14-36% at 6 months<sup>87</sup>.

<sup>81</sup>. Kerr IB, Taylor D. Acute disturbed or violent behaviour: principles of treatment. *Journal Psychopharmacol.* 1997;11:271-9.

<sup>82</sup>. Schwartz TL, Masand PS. The Role of Atypical Antipsychotics in the Treatment of Delirium. *Psychosomatics.* 2002;43:171-174.

<sup>83</sup>. Sirois F. Delirium: 100 cases. *Can Journal Psychiatry.* 1988;33:375-378.

<sup>84</sup>. Koponen H, Stenback U, Mattila E, et al. Delirium among elderly persons admitted to a psychiatric hospital: Clinical course during the acute stage and one-year follow-up. *Acta Psychiatr Scand.* 79:579-585.

<sup>85</sup>. Meagher DJ. Delirium: optimising management. *British Medical Journal.* 2001;vol. 322:20; p144-148.

<sup>86</sup>. Liptzin B. Delirium. In J Sadavoy, LW Lazarus, LF Jarvik, et al (Eds). *Comprehensive Review of Geriatric Psychiatry* (second edition). Washington DC: American Psychiatric Press, 1996.

<sup>87</sup>. Cole G. Delirium in Elderly Patients. *American Journal Geriatric Psychiatry.* 2004;12:7-21.

### LEARNING OBJECTIVES

- Describe the clinical features of the neuroleptic malignant syndrome
- Outline the process of diagnosis of the neuroleptic malignant syndrome
- Describe the treatment of the neuroleptic malignant syndrome

## Neuroleptic Malignant Syndrome

### Introduction

The neuroleptic malignant syndrome (NMS) is a rare but potentially lethal complication of antipsychotic treatment. NMS is estimated to have an incidence of between 0.02 to 3.23% of psychiatric inpatients receiving antipsychotic medication<sup>88</sup>. NMS is twice as common in men and all D2 blocking agents, including antiemetics such as metoclopramide and prochlorperazine are implicated. It has been described with use of all classes of antidepressants, and with abrupt discontinuation of anti-parkinsonian medication. There have also been reports of NMS occurring spontaneously in neurological conditions and schizophrenic illnesses. The pathophysiology is largely unknown, although sudden disruption of dopaminergic activity in the striatum and hypothalamus appear to produce diffuse muscle rigidity leading to raised core body temperature, rhabdomyolysis and accompanying disturbances in physiology<sup>89</sup>. The risks for NMS are shown in Table 1.

1. High doses of neuroleptics
2. Rapid escalation of dose
3. Dehydration
4. Past History of NMS
5. Affective disorder
6. Organic brain syndrome

Table 1 – Risk factors for development of NMS

### Clinical Features of NMS

The clinical features of NMS are shown in Table 2. In essence, any patient taking antipsychotic medication who exhibits fever, rigidity or confusion should have NMS excluded.

1. Hyperthermia
2. Rigidity or other extrapyramidal symptoms
3. Autonomic dysregulation
4. Tachypnoea
5. Confusion or florid delirium
6. Rhabdomyolysis and myoglobinuria
7. Leukocytosis
8. Marked elevation of serum creatine kinase

Table 2 – Features of NMS

<sup>88</sup>. Lazarus A, Mann SC, Caroff SN. *The Neuroleptic Malignant Syndrome and Related Conditions*. Washington, DC, American Psychiatric Press, 1989.

<sup>89</sup>. Stoudemire A, Luther JS. Neuroleptic malignant syndrome and neuroleptic-induced catatonia: differential diagnosis and treatment. *International Journal of Psychiatry in Medicine*. 1984;14:57-63.

### Laboratory Investigations

The critical investigation is the serum levels MM fraction of creatine phosphokinase (CPK). Levels are often markedly elevated. CPK levels may be altered by IM injection and physical trauma during an episode of psychosis. In addition to raised CPK, the patients white cell count is often significantly raised. Given dehydration and sepsis may be comorbidly present, serum electrolytes and screening for infection are often required. Myoglobin may be present in the urine, warranting closer monitoring of renal function and fluid balance.

### Differential Diagnosis of NMS

The differential diagnosis of NMS is shown in Table 3.

1. Serotonin Syndrome
2. Malignant Hyperthermia
3. Lethal Catatonia
4. Sepsis
5. Anticholinergic agent intoxication
6. Overdose of CNS stimulants including MDMA, Amphetamine, Cocaine
7. Delirium of other cause

Table 3 – Differential Diagnosis of NMS

Malignant hyperthermia is a hypermetabolic state of skeletal muscle most frequently associated with the administration of halogenated inhalation anaesthetic agents and succinylcholine. It is heritable, and whilst originally thought to be transmitted via an autosomal dominant trait, it is now considered to have a multifactorial pattern of inheritance. The clinical presentation of malignant hyperthermia is identical NMS. The main clinical differentiation is the context of general anaesthesia via halogenated inhaled anaesthetics. The diagnosis of malignant hyperthermia (or of the latent trait) is reliably established by exposing biopsied muscle tissue to caffeine or halothane in vitro, which results in a hypercontractile response when compared with normal muscle. Treatment of malignant hyperthermia is through the use of dantrolene sodium. Muscle tissue from patients with neuroleptic malignant syndrome does not demonstrate a hypercontractile response to caffeine or halothane. Family histories of patients with malignant hyperthermia have not been documented in patients with neuroleptic malignant syndrome, and the conditions do not seem to be related. Lethal catatonia is a syndrome in which mutism, extreme motor excitement, clouding of consciousness, and fever may progress to severe autonomic disturbances, stupor and coma, and death. It may be a condition related to NMS.

### Clinical Course

NMS is usually present for 2–14 days. Mortality from the condition is reducing with improved critical care. Prior to 1984 the mortality rate for NMS was 25%. Since 1984 it is 11.6%<sup>90</sup>. NMS may be complicated by contractures, renal failure, hypostatic complications such as deep venous thrombosis or pneumonia. There is evidence that prolonged hyperthermia may lead to cerebellar damage<sup>91</sup>.

<sup>90</sup>. Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. *Journal of Clinical Psychiatry*. 1989;50:18-25.

<sup>91</sup>. Lee S, Merriam A, Kim TS, et al. Cerebellar degeneration in neuroleptic malignant syndrome: neuropathologic findings and review of the literature concerning heat-related nervous system injury. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1989;52:387-391.

### Treatment of NMS

Treatment of NMS is based upon prompt recognition of the syndrome, the cessation of antipsychotic treatments agent and lithium (if co-administered). Supportive care is usually provided in critical care setting, with monitoring of fluid balance, renal function and the use of antipyretic agents. ECT has proven efficacy in the treatment of NMS and may be used in severe or refractory cases, particularly where NMS may be related to the use of long acting injectable antipsychotic medication. Anticholinergic agents, intravenous dantrolene and dopamine agonists such as bromocriptine, amantadine, and apomorphine have anecdotal benefits. If clinically indicated, patients who suffer NMS may be rechallenged with antipsychotic medication, ideally of a different class. The likelihood of recurrence of NMS is substantially lower if the antipsychotic rechallenge is >5 days<sup>92</sup>. Patients should only be rechallenged with antipsychotic medications under close medical supervision with regular monitoring of vital signs, serum CPK and frequent neurological investigation.

#### LEARNING OBJECTIVES

- Describe the clinical features of the serotonin syndrome
- Identify the various psychotropic drug interactions that may produce the serotonin syndrome.

## The Serotonin Syndrome

### Introduction

The serotonin syndrome is the result of overstimulation of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptors in central grey nuclei and the medulla. The syndrome is potentially fatal and has increased in significance since the introduction of newer antidepressant and antipsychotic drugs which affect the serotonin neurotransmitter systems.

### Pathogenesis of the serotonin syndrome

The circumstances in which the serotonin syndrome emerges are shown in Table.1

Mechanism	Agents
<ul style="list-style-type: none"> <li>• Excess of precursors of serotonin or its agonists</li> </ul>	Buspirone, L-dopa, lithium, LSD, Ltryptophan, Trazodone
<ul style="list-style-type: none"> <li>• Increased release of serotonin</li> </ul>	Amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, reserpine
<ul style="list-style-type: none"> <li>• Reduced reuptake of serotonin</li> </ul>	SSRI, TCA, trazodone, venlafaxine, meperidine
<ul style="list-style-type: none"> <li>• Slowing down of serotonin Metabolism</li> </ul>	MAOI, e.g., isocarboxazid, selegiline
<ul style="list-style-type: none"> <li>• Ectopic production of serotonin</li> </ul>	Carcinoid syndrome

Table 1 – Pathogenesis of the serotonin syndrome

<sup>92</sup> Wells AJ, Sommi RW, Crismon ML. Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. *Drug Intelligence and Clinical Pharmacy*. 1988;22:475-480.

### Diagnosis of the serotonin syndrome

The diagnostic criteria of the serotonin syndrome are shown in Table 2<sup>93</sup>.

<i>Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms plus 2 minor ones:</i>
<b>Mental (cognitive and behavioural) symptoms</b>
– Major symptoms: confusion, elevated mood, coma or semicoma – Minor symptoms: agitation and nervousness, insomnia
<b>Autonomic symptoms</b>
– Major symptoms: fever, hyperhidrosis – Minor symptoms: tachycardia, tachypnea and dyspnea, diarrhea, low or high blood pressure
<b>Neurological symptoms</b>
– Major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia – Minor symptoms: impaired co-ordination, mydriasis, akathisia

Table 2 – Clinical features of the serotonin syndrome

### Differential Diagnosis of Serotonin Syndrome

The differential diagnosis of the serotonin syndrome is shown in Table 3

<ol style="list-style-type: none"> <li>1. Neuroleptic malignant syndrome</li> <li>2. CNS or systemic Infectious causes</li> <li>3. Other toxic encephalopathy</li> <li>4. Heat stroke</li> <li>5. Delirium tremens</li> <li>6. Anticholinergic delirium</li> </ol>
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Table 3 – The differential diagnosis of serotonin syndrome

### Management

There is no definitive management of NMS other than supportive measures

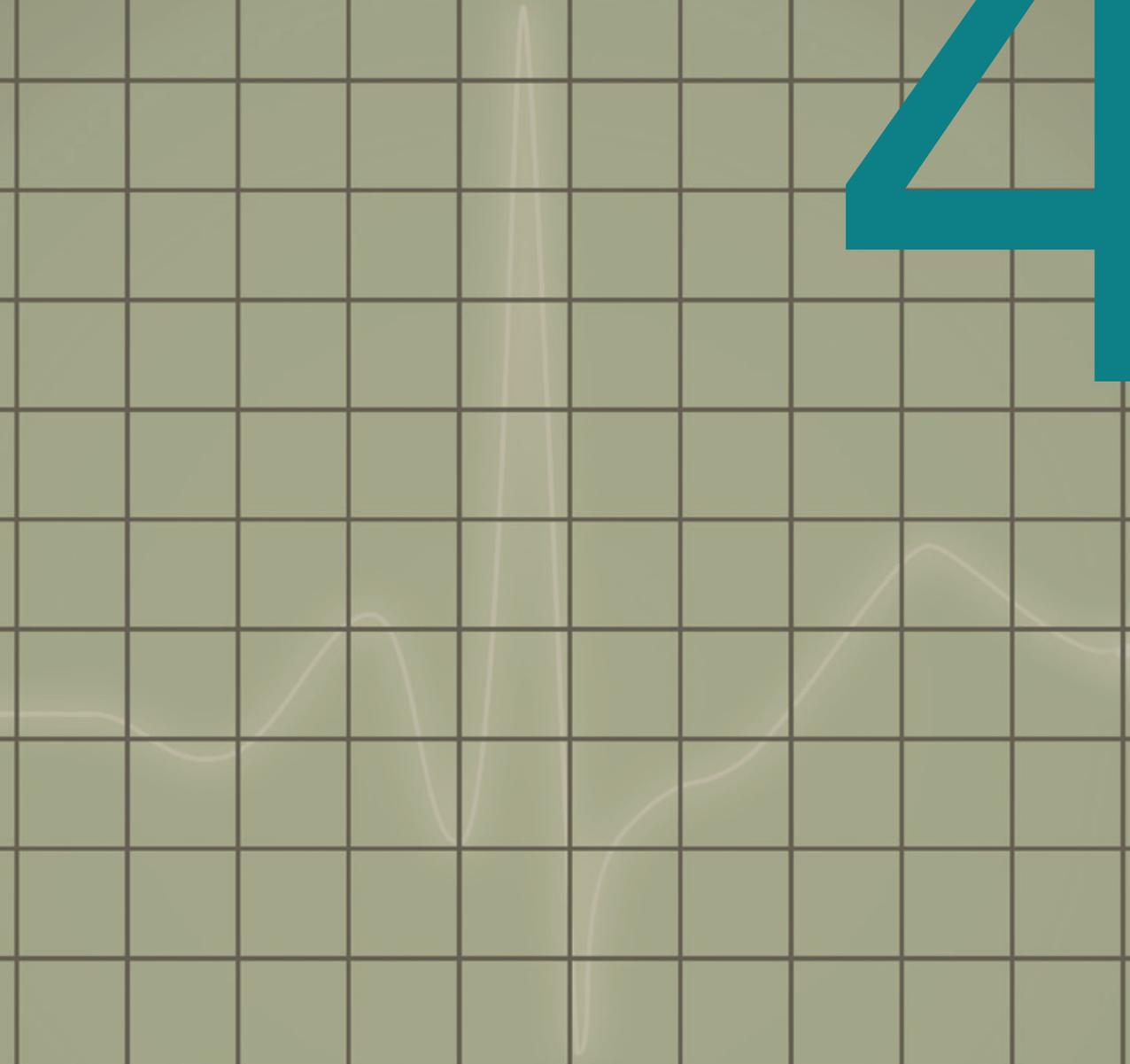
### Outcome

60% of cases resolve within 24 hours. The length of the syndrome is usually dependant upon the  $t_{1/2}$  of the psychotropic drug involved.

<sup>93</sup> Radomski JW, Dursun SM, Revely MA, Kutcher SP. An exploratory approach to the serotonin syndrome; an update of clinical phenomenology and revised diagnostic criteria. *Med Hypotheses*. 2000;55:218-24.



# 4



# 4

## Complications

### LEARNING OBJECTIVES

- Identify the metabolic complications of antipsychotic treatment
- Describe the prevalence and features of the metabolic syndrome in psychiatric populations
- Outline the principles of management of the metabolic syndrome in psychiatric populations

## Metabolic complications of antipsychotic treatment

### Schizophrenia and Metabolic Complications

Up to 51% of males and 64% of females suffering from schizophrenia are obese (defined as BMI > 90th percentile). This is in contrast to 33% of individuals with other psychiatric diagnoses<sup>94</sup>. Ischaemic Heart Disease (IHD) is a greater cause of mortality in psychiatric patients than suicide. Moreover, the IHD mortality rate amongst people suffering schizophrenia has not trended down as it has in the general population<sup>95</sup>. People with mental illness had a higher prevalence of cardiovascular risk factors such as smoking, obesity, lack of exercise, alcohol consumption and salt intake when compared with control subjects from a community-based sample<sup>96</sup>. It is a sad paradox that patients whose psychiatric symptoms respond best are also those most likely to gain weight as a consequence of treatment with antipsychotic medication<sup>97</sup>. Being female, younger, and with a lower pre-treatment BMI and non-Anglo-Celtic ethnicity appear to elevate risk<sup>98</sup>.

Clozapine and olanzapine are associated with the greatest risk of clinically significant weight gain, with other agents producing relatively lower levels of risk. Risperidone, quetiapine, amisulpride and zotepine generally show low to moderate levels of mean weight gain and a modest risk of clinically significant increases in weight. Ziprasidone and aripiprazole treatment are generally associated with minimal mean weight gain<sup>99</sup>. One study found 32% of olanzapine-treated patients

<sup>94</sup>. Dinan TG (ed.). Schizophrenia and diabetes 2003: an expert consensus meeting. *British Journal Psych.* 2004;184:(suppl 7):S53-S114.

<sup>95</sup>. Lawrence DM, Holman CDJ, Jablensky AV, et al. Death rate from ischaemic heart disease in Western Australian psychiatric patients 1980-1998. *British Journal Psychiatry.* 2003;182:31-6.

<sup>96</sup>. Davidson S, Judd F, Jolley D, et al. Cardiovascular risk factors for people with mental illness. *Australian New Zealand Journal Psychiatry.* 2001;35:196-202.

<sup>97</sup>. Czobor P, Volavka J, Sheitman B, et al. Antipsychotic – induced weight gain and therapeutic response: a differential association. *Journal Clinical Psychopharmacol.* 2002;22:244-51.

<sup>98</sup>. McIntyre RS, Mancini DA, Basile VS, et al. Antipsychotic-induced weight gain: bipolar disorder and leptin. *Journal Clinical Psychopharmacol.* 2003;23:323-7.

<sup>99</sup>. Newcomer J W. 2005. "Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review." *CNS Drugs.* 19(Suppl 1):1-93.

possessed the 'atherogenic' metabolic triad comprising hyperinsulinaemia, increased apolipoprotein B concentration, and small, dense LDL, compared with a figure of 5% in risperidone-treated patients<sup>100</sup>.

Data from the National Institute of Mental Health-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)<sup>101</sup> found a prevalence of metabolic syndrome of 42.7%. The mean BMI of the subjects was 29.7 (SD=7.0). Among fasting subjects, 44.4% met criteria for the metabolic syndrome. The risk of metabolic syndrome in people suffering schizophrenia is 2–3 times that of the general population.

#### Putative mechanisms of metabolic consequences of antipsychotic treatment

There are a variety of theoretical models of the mechanism of weight gain related to antipsychotic therapy. Apart from the effects of illness on lifestyle there is the possibility of an intrinsic propensity to weight gain in schizophrenia. Stimulation of Histamine 1 receptors may trigger hunger or impair satiety in people taking medications such as clozapine or olanzapine. Insulin resistance, and a propensity to glucose intolerance can occur as a consequence of multiple intercurrent effects of the antipsychotics including the effects of increased body mass and direct interference by of the antipsychotics in the glucose metabolism<sup>102</sup>, in particular interference with hepatic glycogen synthesis through alteration of hepatocyte 5HT receptors<sup>103</sup>. The induction of peripheral insulin resistance and the direct influence on pancreatic beta-cell function by 5-HT<sub>1A/2A/2C</sub> receptor antagonism, or by inhibitory effects via alpha 2-adrenergic receptor is a postulated mechanism<sup>104</sup>. There has been recent interest in, three recently identified cytokines which play crucial roles in the regulation of energy balance and glucose metabolism – ghrelin, adiponectin and leptin<sup>105</sup>. Adipocyte expression or secretion of adiponectin an insulin-sensitizing cytokine is affected by olanzapine<sup>106</sup>.

The criteria proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), with minor modifications, are currently recommended and widely used<sup>107</sup>. The American Heart Association and the National Heart, Lung, and Blood Institute recommend that the metabolic syndrome be identified as the presence of three or more of these components. The metabolic syndrome is characterized by a group of metabolic risk factors in one person (Table 1).

- 
- <sup>100</sup> Bouchard RH, Demers M, Simoneau I, et al. Atypical antipsychotics and Cardiovascular Risk in Schizophrenic patients. *Journal Clinical Psychopharmacol.* 2001;21:110-11.
- <sup>101</sup> McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Scott Stroup T, Lieberman JA. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80:19-32.
- <sup>102</sup> Filakovic P, Koic O, et al 2007. "Second generation antipsychotics and risk of diabetes type II – comparison between olanzapine and risperidone." *Coll Antropol.* 31(4):1105-9.
- <sup>103</sup> Hampson LJ, Mackin P, et al 2007. "Stimulation of glycogen synthesis and inactivation of phosphorylase in hepatocytes by serotonergic mechanisms, and counter-regulation by atypical antipsychotic drugs." *Diabetologia.* 50(8):1743-51.
- <sup>104</sup> Schwenkreis P, Assion HJ, 2004. "Atypical antipsychotics and diabetes mellitus." *World Journal Biol Psychiatry.* 5(2):73-82.
- <sup>105</sup> Hosojima H, Togo T, et al 2006. "Early effects of olanzapine on serum levels of ghrelin, adiponectin and leptin in patients with schizophrenia." *Journal Psychopharmacol.* 20(1):75-9.
- <sup>106</sup> Richards A A, Hickman IJ, et al 2006. "Olanzapine treatment is associated with reduced high molecular weight adiponectin in serum: a potential mechanism for olanzapine-induced insulin resistance in patients with schizophrenia." *Journal Clinical Psychopharmacol.* 26(3):232-7.
- <sup>107</sup> National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (final report). *Circulation.* 2002;106:3143-421.

1. Abdominal obesity (excessive fat tissue in and around the abdomen)
2. Atherogenic dyslipidemia (blood fat disorders — high triglycerides, low HDL cholesterol and high LDL cholesterol — that foster plaque build-ups in artery walls)
3. Elevated blood pressure
4. Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
5. Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor-1 in the blood)
6. Proinflammatory state (e.g., elevated C-reactive protein in the blood)
7. Elevated waist circumference: Men — Equal to or greater than 102 cm  
Women — Equal to or greater than 88 cm
8. Elevated triglycerides: Equal to or greater than 150 mg/dL
9. Reduced HDL (“good”) cholesterol: Men — Less than 40 mg/dL  
Women — Less than 50 mg/dL
10. Elevated blood pressure: Equal to or greater than 130/85 mm Hg
11. Elevated fasting glucose: Equal to or greater than 100 mg/dL

Table 1 – Features of the metabolic syndrome

### Glucose Regulation, Diabetes, Adiposity, and Dyslipidemia

Type I diabetes, which accounts for less than 10% of diabetes cases, often begins in childhood and is usually the result of autoimmune destruction of the insulin-secreting pancreatic beta cells. Type II diabetes, which usually begins after age 45, is characterized by two pathological processes: inadequate insulin secretion and impaired insulin action at the insulin receptor, or insulin resistance. Early in the course of type 2 diabetes, insulin resistance, caused by genetic and/or environmental factors, evokes a compensatory increase in pancreatic insulin secretion so that glycaemic control is maintained; insulin levels are elevated, but random and fasting plasma glucose levels remain normal. Insulin resistance and compensatory hyperinsulinaemia are typically associated with elevated fasting triglyceride levels, low levels of high-density lipoprotein (HDL) cholesterol, and elevated levels of atherogenic low-density lipoprotein (LDL) cholesterol particles. Over a period of 7 to 10 years on average, increasing insulin resistance and/or deteriorating beta cell function leads to a state in which pancreatic compensatory capacity is overwhelmed<sup>108</sup>.

Insulin insufficiency is first evident as postprandial hyperglycaemia (or an abnormal glucose tolerance test) due to impaired uptake of glucose into muscle. Later in the course of the disease, with progressive loss of insulin secretion, liver glucose production becomes dysregulated, resulting in fasting hyperglycaemia. At this relatively advanced illness stage, an elevated fasting plasma glucose level allows detection of “prediabetes” or type II diabetes. Type 2 diabetes is diagnosed by measurement of fasting plasma glucose level using thresholds for diabetes (>125 mg/dl) and prediabetes (100–125 mg/dl) defined by the American Diabetes Association<sup>15</sup>.

With progressive beta cell failure, disinhibition of inhibition of lipolysis increases, further reducing control over free fatty acid release and worsening the characteristic dyslipidemia associated with diabetes. Physiological stress, such as intercurrent illness in the presence of marked impairment in insulin secretory functioning and insulin resistance, can result in severe hyperglycaemia, which can acutely inhibit beta cell function, a state known as glucose toxicity. Under these circumstances, acute glycaemic decompensation may result in diabetic coma and death due to extreme hyperglycaemia with excessive fatty acid and ketone formation (diabetic ketoacidosis) or non-ketotic hyperosmolar states.

<sup>108</sup> American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;27(suppl 1):S5-S10.

Insulin resistance and type II diabetes occur most often in the context of overweight and obesity, particularly excess abdominal adiposity. Adiposity and fitness are each thought to contribute about 30% of the individual variance in insulin resistance, with genetic factors accounting for the remainder<sup>109</sup>. Thus, while excessive abdominal adiposity is significantly related to risk of insulin resistance and diabetes, type II diabetes can also occur in the absence of overweight or obesity.

### Management of Metabolic Syndrome

The Adult Treatment Panel III treatment guidelines<sup>110</sup> recommend therapeutic life style changes, including reduced intake of saturated fats and cholesterol, increased fibre intake, weight reduction, and increased physical activity as the first-line therapeutic approach to the risk of cardiovascular disease. LDL-lowering drugs, including HMG-CoA reductase inhibitors (statins), bile acid sequestrants, nicotinic acid, and fibric acids, are prescribed as needed to achieve target LDL levels.

The metabolic syndrome increases the risk of cardiovascular disease at any given level of LDL and is considered a secondary target of risk-reduction therapy after lowering LDL cholesterol. The Adult Treatment Panel III guidelines identify obesity as the primary target of treatment of the metabolic syndrome and weight loss and increased physical activity as the first-line treatment approaches. Weight loss lowers LDL cholesterol and triglycerides, increases HDL cholesterol, lowers blood pressure, and reduces insulin resistance. Metformin reduces insulin resistance, reduces new-onset coronary heart disease in obese patients with diabetes, and prevents or delays type II diabetes in patients with impaired glucose tolerance. Insulin sensitizers of the thiazolidinedione class also prevent or delay type 2 diabetes in at-risk patients. Antipsychotics and meet criteria for the metabolic syndrome should be treated with therapeutic life style changes and medications in accordance with hypertension guidelines. Finally, low-dose aspirin may be indicated to mitigate the prothrombotic state in patients with metabolic syndrome at elevated risk of coronary heart disease.

### LEARNING OBJECTIVES

- Understand the importance of abnormalities of QTc interval
- List psychotropic treatments which can alter the QTc interval
- Describe the risk of sudden death in patients with severe mental illness

## QTc abnormalities and psychotropic treatment

### Introduction

The QT interval is an ECG measure that includes both depolarization and repolarization. It begins with the onset of ventricular depolarization (Q wave) and ends with completion of repolarization (T wave). Because the QT interval shortens with increasing heart rates, it is usually corrected for heart rate (QTc). QTc intervals are usually around 400 msec in duration, and values lower than 440 are considered normal (Fig 1). A QTc >500 msec has frequently been used as a cutoff because longer QTc interval measures are associated with substantially higher risk of cardiac arrhythmias.

<sup>109</sup> Reaven G. The metabolic syndrome: is this diagnosis necessary? *American Journal Clinical Nutr.* 2006;83:1248-1251.

<sup>110</sup> Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.

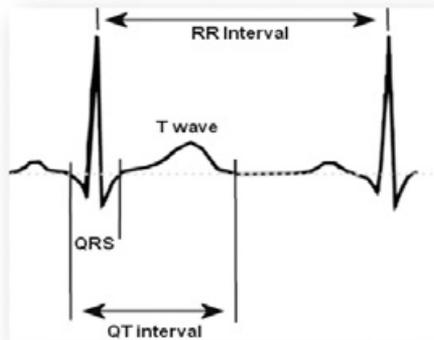


Figure 1 – The normal ECG complex from the P-T waves

### A brief review of the physiology of cardiac conduction

Depolarization of ventricular myocardial cells is the result of a rapid influx of  $\text{Na}^+$  ions through selective  $\text{Na}^+$  channels. Repolarization occurs via cationic inflows through  $\text{Ca}^{++}$ ,  $\text{Na}^+$ , and several  $\text{K}^+$  channels, including the hERG gene coded  $\text{I}_{\text{Kr}}$  potassium channel (a complex of 4 identical subunits each containing 6 transmembrane domains, numbered S1-S6, a pore helix and a slide helix). This process is reflected on the ECG by the QRS interval. The hERG/ $\text{I}_{\text{Kr}}$  channel is the most critical in drug-induced QTc prolongation syndromes. There are 10 described heritable forms of the Long QT Syndrome (LQTS). Drugs which blocking the  $\text{I}_{\text{Kr}}$  channel prolong the QTc interval and can induce life threatening cardiac arrhythmias, the most significant of which is 'torsade de pointes'. Sudden death in apparently healthy adults can occur as a result of drug induced QTc prolongation<sup>111</sup>. Prolonged QTc intervals are associated with the risk of sudden death after myocardial infarction and the LQTS. In some forms of inherited LQTS, sudden death can occur as a consequence of exercise, sleep or emotional shock. QTc interval prolongation is the "clinical red flag" that warns of the possibility of torsade de pointes and sudden death.

### Torsade de Pointes

Torsade de pointes meaning "twisting around the point" (a reference to a ballet movement) refers to an uncommon variant of ventricular tachycardia (VT) in which the QRS complexes twist about the isoelectric axis of the ECG. The morphology of the QRS complexes varies from beat to beat. The ventricular rate can range from 150-250 beats per minute (Fig 2).

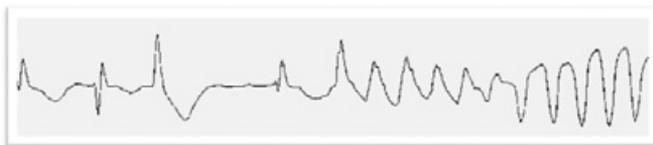


Figure 2 – Torsade de pointes

The QTc interval is a modest predictor of torsade de pointes. The underlying basis for the arrhythmia is delay in phase III of the myocardial action potential mediated by the  $\text{I}_{\text{Kr}}$  potassium channel. This prolonged period of repolarization and the irregularity of repolarization times among different myocardial fibres create re-entrant phenomena or ectopic electrical activity to occur, producing the arrhythmia. As the underlying aetiology and management of torsade are, in general, quite different from VT, the management of torsade with group IA antiarrhythmic drugs can be lethal.

<sup>111</sup>. Witchel HJ, Hancox JC. Familial and acquired long QT syndrome and the cardiac rapid delayed rectifier potassium current. *Clin Exp Pharmacol Physiol.* 2000;27:753-76.

### Psychotropic Medications and abnormalities of the QTc

Not all drugs that prolong the QTc interval produce torsade de pointes and sudden death. Tricyclic antidepressants, for example, have a 'quinidine like effect'<sup>112</sup> and block the Na<sup>+</sup> inflow channel, and, as a result, slow depolarization and widen both the QRS and the QTc intervals. Thioridazine blocks hERG channel, is more often associated with sudden death in otherwise healthy individuals through cases of torsade de pointes. Psychotropic medications associated with prolonged QTc and torsade de pointes are shown in Table 1.

Prolonged QTc and torsade de pointes
<ul style="list-style-type: none"> <li>• Thioridazine</li> <li>• Ziprasidone</li> <li>• Pimozide</li> <li>• Amisulpiride</li> <li>• Droperidol</li> <li>• Sertindole</li> </ul>
Prolonged QTc and possible torsade de pointes*
<ul style="list-style-type: none"> <li>• Olanzapine</li> <li>• Quetiapine</li> <li>• Risperidone</li> <li>• Chlorpromazine</li> <li>• Clozapine</li> <li>• Haloperidol</li> </ul>
<i>*high dose or drug interactions</i>

Table 1 – Antipsychotic Drugs and the propensity for torsade de pointes

Other medication classes including antiarrhythmic, tricyclic antidepressants, antihistamines, and antibiotics are associated with QT prolongation syndromes and must be used with care in combination with antipsychotic medications implicated in QT prolongation.

### Assessment for Risk of QTc Prolongation and torsade

The risk factors for prolonged QTc and torsade de pointes and suggested screening procedures (in addition to identification of risk factors in the clinical history) are shown in Figure 3. Assessment of a patient's vulnerability to develop potentially fatal QT prolongation syndromes should include identification of these risk factors.

<sup>112</sup> Lipscomb PA. Cardiovascular side effects of phenothiazines and tricyclic antidepressants: a review. *Postgrad Med.* 1980;67:189-19.

<p><b>Previous QT abnormality</b> (12-lead ECG)</p>	<p><b>Familial History of LQTS</b></p>	<p><b>Low serum K<sup>+</sup>, Mg<sup>++</sup> or Ca<sup>++</sup></b> (Serum Electrolytes)</p>
<p><b>Alcohol Abuse</b> (LFTs, MCV, CDT)</p>	<p><b>Anorexia Nervosa</b> (BMI)</p>	<p><b>Hypothyroidism</b> (Thyroid function)</p>

Table 1 – Antipsychotic Drugs and the propensity for torsade de pointes

### Sudden Death in Mentally Ill Populations

There is considerable evidence in the scientific literature that people suffering schizophrenia are at higher risk for sudden death. This is both related to antipsychotic treatment<sup>113</sup>, and independent of this variable<sup>114</sup>. Cardiovascular risk factors are covered in a separate section, however it is important to note that chronic mental illness is associated with the lifestyle risk factors for ischaemic heart disease. It is also evident that people with chronic mental illnesses have, for a variety of reasons, less access to early intervention in physical disease.

#### LEARNING OBJECTIVES

- Describe the features of akathisia
- Describe the treatment of akathisia
- Understand the risks and features of tardive dyskinesia

## Akathisia and tardive dyskinesia

### Akathisia

“Akathisia” is a drug-induced movement disorder, which presents as a syndrome of motor restlessness, usually in the lower extremities, often accompanied by a subjective sense of inner restlessness, and dysphoria<sup>115</sup>. The term derives from the Greek ακάθιδις, meaning “without sitting”. Akathisia exists in acute, chronic (duration >3 months) and tardive forms (with onset (>3 months). A form of withdrawal akathisia may occur as a consequence of a reduction in the dose of antipsychotic medication<sup>116</sup>. A syndrome resembling akathisia is seen following the initiation of treatment with aripiprazole, although this is an “activation” syndrome arising from partial D<sub>2</sub> receptor agonism in the striatum.

<sup>113</sup> Ray W, Meredith S, Purushottam B, et al. Antipsychotics and the Risk of Sudden Cardiac Death. *Arch Gen Psychiatry*. 2001;58:1161-1167.

<sup>114</sup> Davidson M. Risk of cardiovascular disease and sudden death in schizophrenia. *Journal Clinical Psychiatry*. 2002;63:5-1.

<sup>115</sup> Barnes TR, Braude WM. Akathisia variants and tardive dyskinesia. *Arch Gen Psychiatry*. 1985;42:874-878.

<sup>116</sup> Sachdev P. Research diagnostic criteria for drug-induced akathisia: conceptualization, rationale, and proposal. *Psychopharmacology*. 1994;114:181-186.

The incidence of acute akathisia amongst patients taking antipsychotic medication is 31%<sup>117</sup> and the prevalence rate ranges up to 41%<sup>118</sup>. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, there were no significant differences between first and second-generation antipsychotics in the incidence of extrapyramidal symptoms, although the rate of discontinuation of treatment was significantly higher for perphenazine, the only First Generation Antipsychotic studied<sup>119</sup>. There is no parallel between the concurrent severity of akathisia and other extrapyramidal side-effects of antipsychotic medication, implying that akathisia is a different phenomenon from the other recognised extrapyramidal side-effects of neuroleptic medication. Akathisia has been described in patients taking SSRI antidepressants. Moreover, the lower propensity or serotonin blocking Second Generation Antipsychotics implies a serotonergic mechanism involved in the genesis of akathisia. Cholinergic and adrenergic pathways are also implicated<sup>120</sup>.

The risk Factors for akathisia are shown in Table 1.

Higher dosages of neuroleptic medication	Demographic	Clinical Features
<ul style="list-style-type: none"> <li>• Rapid rate of increase of dosage</li> <li>• Use of higher-potency FGA medication</li> </ul>	<ul style="list-style-type: none"> <li>• Older age</li> <li>• Female sex</li> </ul>	<ul style="list-style-type: none"> <li>• Prominent negative symptoms</li> <li>• Iron deficiency</li> <li>• Cognitive dysfunction</li> <li>• Affective disorder</li> </ul>

Table 1 – Risk factors for akathisia

### Assessment of akathisia

The diagnosis of akathisia is primarily clinical. Observations of motor restlessness in a patient taking antipsychotic or SSRI medication are the commonest clinical sign, although akathisia can present as a primarily subjective sense of restlessness, variably described by the patient as agitation, dysphoria or anxiety. The Barnes Akathisia Rating Scale can also be used to formally assess akathisia<sup>121</sup>. Akathisia should be differentiated from psychotic agitation or psychomotor agitation in severe melancholic depression. Anxiety can be mistaken for akathisia. Some features of tardive dyskinesia, particularly truncal or limb movement, can be confounded for akathisia. Other neurological disorders producing choreo-athetoid movements can resemble akathisia. There is a possible relationship between akathisia and the “Restless Legs Syndrome”. This condition is characterized by lower body movement similar to those seen in akathisia, although the symptoms usually occur only during rest, relaxation or sleep, and tend to follow a circadian pattern<sup>122</sup>.

<sup>117</sup> Sachdev P. *Akathisia and Restless Legs*. New York, Cambridge University Press, 1995.

<sup>118</sup> Sachdev P. The epidemiology of drug-induced akathisia. II: chronic, tardive, and withdrawal akathisias. *Schizophr Bull*. 1995;21:451-461.

<sup>119</sup> Lieberman JA, Stroup TS, McEvoy, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal Medicine*. 2005; 353:1209-1223.

<sup>120</sup> Sachdev PS, Brune M. Animal models of acute drug-induced akathisia: a review. *Neurosci Biobehav Rev*. 2000;24:269-277.

<sup>121</sup> Barries TR. A rating scale for drug-induced akathisia. *British Journal Psychiatry*. 1989;154:672-676.

<sup>122</sup> Kushida CA. Clinical presentation, diagnosis, and quality of life issues in restless legs syndrome. *American Journal Medicine*. 2007;120(suppl 1):S4-S12.

### Treatment of akathisia

Akathisia is a sinister symptom, and strongly correlates with medication noncompliance<sup>123</sup>, worsening of psychotic symptoms, impulsive behaviour, increased liability for aggression, deliberate self-harm and completed suicide<sup>124</sup>. Reduction of dose of the patient's neuroleptic medication, or changing the patient's treatment to a different agent with a lower propensity for such side effects are the first line measures for treatment. If this is not appropriate, benzodiazepines, propranolol, or anticholinergic medications may be of some help in treating acute akathisia (Figure 1).

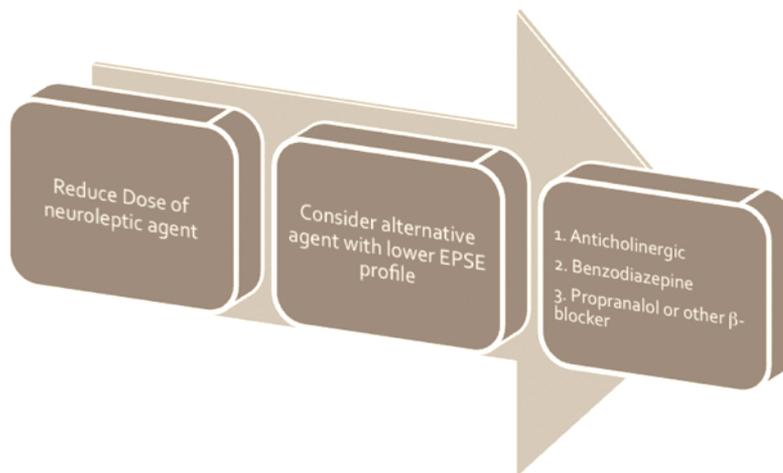


Figure 1 – Management of akathisia

### Tardive Dyskinesia

Tardive Dyskinesia (TD) is a potentially irreversible neurological syndrome characterised by choreo-athetoid movements of the orofacial muscles and, less commonly, truncal and limb muscles. Rare cases of TD involving the diaphragm and pectoral muscles have been described. The prevalence of TD varies from 15-20% in psychiatric patient populations and the risk is cumulative with ongoing exposure to neuroleptic medication. The aetiology of TD is still elusive. The two favoured theories are dopamine supersensitivity in the in the striatum, acquired during chronic neuroleptic exposure and the 'free radical hypothesis' in which accumulation of free radicals produce damage to the striatum.

The risk factors for TD are shown in Figure 1.

Risk Factor	Patient Variable	Treatment Variable
	<ul style="list-style-type: none"> <li>• Age</li> <li>• Female</li> <li>• Diabetes</li> <li>• Mood Disorder</li> <li>• Cognitive Impairment</li> </ul>	<ul style="list-style-type: none"> <li>• Length of treatment</li> <li>• Previous EPSE</li> </ul>

Figure 1 – Risk Factors for tardive dyskinesia

There is no definitive treatment for TD, and the aphorism "There are many treatments for TD and there are none" applies. A recent review<sup>125</sup> considered various proposed treatments including – antioxidants (especially Vitamine E 1000 I.U. daily), Dopamine depleting agents such as

<sup>123</sup>. Van Putten T. Why do schizophrenic patients refuse to take their drugs? *Arch Gen Psychiatry*. 1975;31:67-72.

<sup>124</sup>. Van Putten T, Mutalipassi LR, Malkin MD. Phenothiazine-induced decompensation. *Arch Gen Psychiatry*. 1974;30:13-19.

<sup>125</sup>. Gupta S, Mosnik D, Black D, et al. Tardive Dyskinesia: Review of Treatments Past, Present, and Future. *Annals of Clinical Psychiatry*. 1999;11:257-266.

tetrabenazine, medications acting on GABA receptors such as baclofen and the use of SGAs, in particular clozapine. There is no convincing data to support any one treatment modality in TD.

### Suggested assessment for drug induced movement disorders

Given the clinical significance of all drug induced movement disorders, regular systematic review for the presence of signs of the various conditions should be routinely performed on all patients receiving neuroleptic medications. There are several rating scales available, such as the Abnormal Involuntary Movement Scale (AIMS), however a clinical algorithm for assessment of drug induced movement disorder is proposed below (Figure 3).

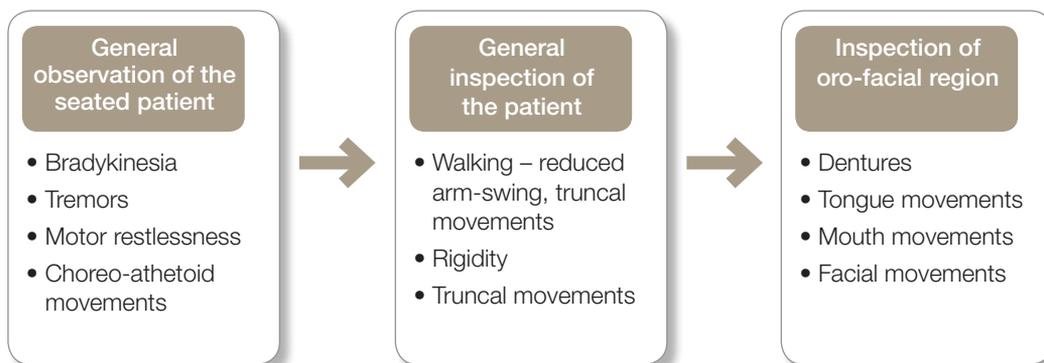


Figure 3 – Approach to the assessment of Drug Induced Movement Disorders.

### LEARNING OBJECTIVES

- Understand the normal physiology of prolactin
- Describe the sequelae of raised levels of serum prolactin
- Identify the propensity for different psychotropic agents to raise serum prolactin

## Hyperprolactinaemia

### Introduction

Elevation of prolactin levels in patients is a frequent and problematic side-effect of the use of psychotropic medication. Hyperprolactinaemia produces undesirable side effects in the short term, affecting medication tolerability and treatment compliance. Longer-term morbidity chronic iatrogenic hyperprolactinaemia is also of concern.

### The Physiology of Prolactin

The normal physiology of prolactin in humans is shown in Figure 1. Prolactin is released from the anterior pituitary gland in a pulsatile manner with up to 15 peaks per 24 hours. The normal physiological range of serum prolactin levels is between 10-25µg/L. Serum prolactin levels exhibit a circadian pattern and usually peak after 4 hours of a sleep cycle. Prolactin has the primary function of lactogenesis via the stimulation of breast tissue and milk synthesis. It suppresses gonadotropin function and likely plays a role in mediating attachment behaviours in humans.

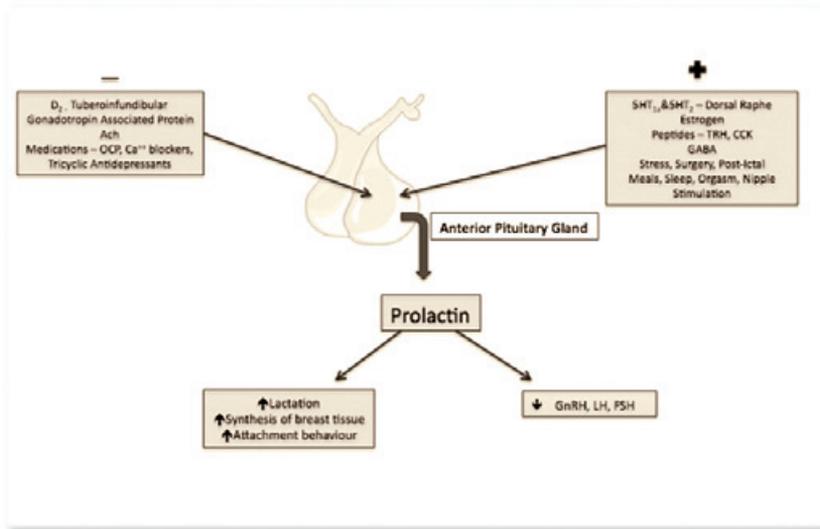


Figure 1 – The normal physiology of prolactin in humans

### The Effects of Hyperprolactinaemia

Cross sectional studies of patients administered neuroleptic medication indicate the prevalence of hyperprolactinaemia is 34% in men and 75% in women<sup>126</sup>. Traditionally, hyperprolactinaemia is considered to be present at levels > 100µ/L, however clinically significant side-effects can emerge at lower levels. Women, particularly in the post-partum period and pubescent children are particularly vulnerable to iatrogenic hyperprolactinaemia. There is some evidence of menstrual irregularities in women with schizophrenia which predate treatment with antipsychotic medication<sup>127</sup>.

#### Short term

Females – Reduced libido, amenorrhoea, galactorrhoea, mastodynia, anovulation, virilising effects, weight gain

Males – Gynaecomastia, reduced spermatogenesis, reduced libido, erectile dysfunction, weight gain

#### Longer term

Many of the longer term consequences of iatrogenic hyperprolactinaemia are speculative and established with variable certainty. There is some evidence to suggest that chronic antipsychotic exposure may be associated with reduced bone density through suppression of sex-steroid function<sup>2</sup>. A recent study found a 16% increase in the risk of breast cancer in women chronically exposed to D2 antagonists<sup>129</sup>. Analysis of the FDA database indicates a possible risk of development of pituitary tumours, particularly with risperidone<sup>130</sup>.

### Antipsychotic Medication and Hyperprolactinaemia

Any medication that effects some blockade at the D2 tuberoinfundibular neuronal cluster has the capacity to elevate serum prolactin. First generation antipsychotic medications, particularly high

<sup>126</sup>. Smith S, O'Keane V, Murray R, et al. Sexual dysfunction in patients taking conventional antipsychotic medication. *British Journal Psychiatry*. 2002;181:49-55.

<sup>127</sup>. Wieck A, Haddad PM. Antipsychotic-induced hyperprolactinaemia in women: pathophysiology, severity and consequences: selective literature review. *British Journal Psychiatry*. 2003;182:199-204.

<sup>128</sup>. Haddad P, Wieck A. Antipsychotic-Induced Hyperprolactinaemia: Mechanisms, Clinical Features and Management. *Drugs* 2004;64:2291-2314.

<sup>129</sup>. Wang PS, Walker AM, Tsuang MT, et al. Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry*. 2002;59:1147-1154.

<sup>130</sup>. Szarfman A, Tonning J, Levine G, et al. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. *Pharmotherapy* 2006;26:748-58.

potency agents, have the greatest potential to increase serum prolactin, whereas some second generation antipsychotics have little propensity, or in the case of aripiprazole may reduce prolactin levels – Table 1.

Medication	Hyperprolactinaemia
<ul style="list-style-type: none"> <li>• FGAs – especially haloperidol, zuclopenthixol, flupenthixol, fluphenazine</li> <li>• Risperidone</li> <li>• Paliperidone</li> <li>• Amisulpiride</li> </ul>	Significant potential (“prolactin raising”)
<ul style="list-style-type: none"> <li>• Ziprasidone</li> <li>• SSRI antidepressants</li> </ul>	Moderate potential
<ul style="list-style-type: none"> <li>• Olanzapine</li> <li>• Quetiapine</li> <li>• Clozapine</li> <li>• Tricyclic antidepressants</li> </ul>	Lower potential (“prolactin sparing”)
<ul style="list-style-type: none"> <li>• Aripiprazole</li> <li>• Amantadine</li> <li>• Bromocriptine</li> </ul>	May reverse

Table 1 – Psychotropic Medication and Hyperprolactinaemia

### Possible Treatment of Hyperprolactinaemia

Once it is established that the cause of hyperprolactinaemia is related to psychotropic use, the treatment of iatrogenic hyperprolactinaemia is based primarily upon clinical considerations. Patients who are concerned about reduced fertility or problematic endocrine related side-effects may warrant consideration of medication change to a prolactin sparing antipsychotic medication, although the strategy of changing agents may be associated with increased risk of relapse<sup>131</sup>. Female patients may benefit from the oral contraceptive pill. The administration of dopaminergic agonists such as bromocriptine is ill-advised due to the potential to worsen psychotic symptoms. Some anecdotal evidence suggests that there is potential benefit to the addition of aripiprazole to existing antipsychotic.

Excessively elevated serum prolactin (>100µg/L) may require further investigations to exclude a general medical illness. See Table 2.

<sup>131</sup> Kim KS, Pae CU, Chae JH, et al. Effects of olanzapine on prolactin levels of female patients with schizophrenia treated with risperidone. *Journal Clinical Psychiatry*. 2002;63:408-13.



# 5

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## Important Legislation

### LEARNING OBJECTIVES

- Outline the rationale for the Mental Health Act
- Describe the processes of referral to Declared Mental Health Facilities
- Understand the provisions for involuntary psychiatric treatment in NSW

### The Mental Health Act (2007)

#### The Rationale for Mental Health Act

The NSW *Mental Health Act 2007* (MHA or 'Act') governs "the care, treatment and control of mentally ill and mentally disordered persons and other matters relating to mental health". The *Act* exists when a person's reason or judgment is impaired by a mental illness – defined as a syndrome characterized by delusions, hallucinations, severe disturbance of thought, or severe disturbance of mood. The critical test for the *Act* is the presence of "risk" to the safety of others or the patient. The latter is expanded as a risk of physical harm or, in the case of severe mood disorder, the risk to a person's reputation or financial interests.

#### Definitions in the Act

In the *Act* a "patient" is defined as a person who is admitted to a Declared Mental Health Facility (DMHF) in accordance with the *Act*. This term applies following the person's admission and applies even if the person is absent (either agreed or unauthorised) from the ward. A patient who has been referred to a DMHF and is awaiting independent review by a magistrate is deemed an "Assessable patient". If a magistrate finds that the person is "mentally ill" in terms of the *Act* and either a treatment order or a deferred discharge is decreed, then the patient is defined as an "Involuntary patient". The *Act* defines an "authorised medical officer" as the medical superintendent of the DMHF or the medical officer, nominated by the medical superintendent.

#### Patient's Rights under the Act

The patient is entitled to the best possible care in the least restrictive environment to enable their treatment to be effective. The impact of treatment on a patient's dignity must be minimal. The patient and his or her family must be provided with information about their rights and the procedures of the *Act*. The treatment choices made under the *Act* must be for the benefit of the patient with the goal of enabling the person to live, work and participate in the community. Where possible, a patient and his or her family, must be notified of treatment options, the risks and likely benefits, and alternative treatment choices.

Under Section 71 of the Act, patients nominate designated “Primary Carers”. These are usually the patient’s guardian, or a child’s parent or a person in a “close and continuing relationship” with a patient or a close relative or friend (defined as a close personal relationship, through frequent personal contact and interest in patient’s welfare). The Primary carer must be notified within 24 hours of person’s detention (s 75); of the proposed mental health inquiry by magistrate (s 76); regarding discharge planning and ongoing treatment (s 79); if the patient is absent without permission/ fails to return from leave (s 78); if the patient is re-classification as a “voluntary patient” or is to be discharged from the DMHF.

**Mentally Disordered Patients**

A person may be admitted to a DMHF if the person’s immediate behaviour is “so irrational as to justify a conclusion on reasonable grounds that temporary care, treatment or control of the person is necessary for the person’s own protection from serious physical harm, or for the protection of others from serious physical harm”. Admission as a mentally disordered patient is limited to three working days, so theoretically could extend for periods of up to 5-6 days over weekends or public holidays. In general, prolonged admissions warrant reconsideration of diagnosis and the appropriate classification under the Act.

**Pathways to Admission**

The various pathways to admission and subsequent assessment process for the Act are shown in Figure 1.

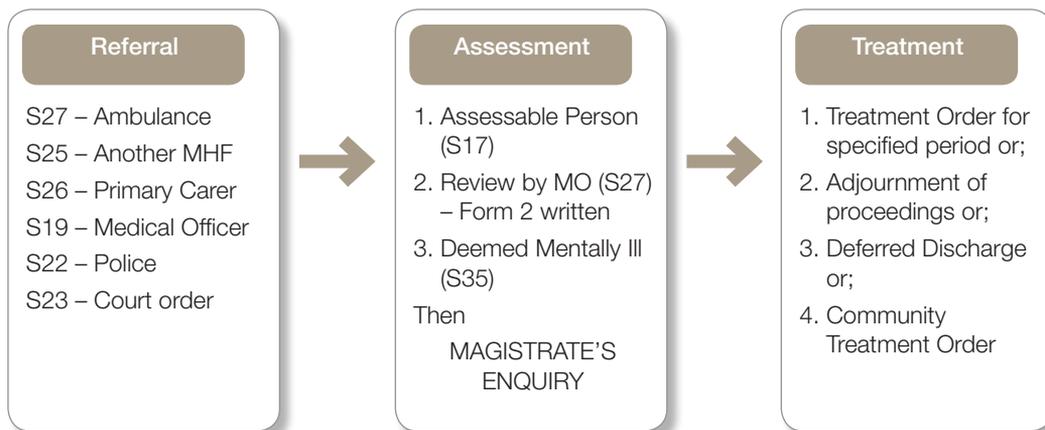


Figure 1 – The pathways to treatment under the *Mental Health Act* (1997)

A person can be conveyed to a Declared Mental Health Facility (DMHF) by police, ambulance, medical officers, the courts or a primary carer in consultation with a mental health service. Once the patient is conveyed to a DMHF they become and ‘assessable person’. The person is assessed by a medical officer under S27 of the Act and is either deemed ‘mentally ill’ (S35) and detained in a DMHF or discharged or offered treatment as a voluntary patient. The patient is now deemed a “mentally ill patient”. The Area Mental Health Service is then obliged to present a case to a magistrate. At that hearing, a *prima facie* case must be made that the patient is ‘mentally ill’ in terms in of the Act and is a risk to either themselves or others. The patient has a legal representative present at the hearing, and the rules of evidence are akin to other court matters. The magistrate makes a legal determination as to whether there is sufficient evidence of the person being mentally ill and that they pose a risk to themselves, others, their finances or their reputation. If these conditions are established the magistrate has the discretionary options of:

- Deferring the patient’s discharge from the DMHF;
- Making a treatment order for involuntary treatment in a DMHF for a specified period;
- Making a Community Treatment Order.

In some instances, the treating clinician may not be in a position to have determined the nature of the patient's problems, they may request the matter be adjourned for a period of up to two weeks.

There are two appellat processes for the patient – the patient may appeal to the Medical Superintendent of the DMHF or to the Mental Health Review Tribunal, an independent body comprising legal, medical and other social representatives.

As an involuntary patient, the patient is given opportunity to nominate a “primary carer”, who is legally entitled to be consulted on a number of matters relating to the care of the patient including:

- Changes to the patient's legal status;
- Substantial changes to the patient's treatment plan;
- Leave provisions;
- Discharge planning

There are circumstances where, if no suitable primary carer can be identified or if the nominated carer is not suitable, that this provision of the *Act* can be reasonably waived.

### Community Treatment Orders

One of the main principles of the *Act* is the requirement to provide treatment under the ‘least restrictive option’. In most instances, the patient will be able to safely and effectively receive psychiatric treatment in a community setting. Involuntary treatment in the community is provided under the provisions of Community Treatment Orders (CTOs) can be sought by Authorised Medical Officers under the *Act*, a medical practitioner familiar with the person's clinical history, a director of community mental health service familiar with the clinical history of the affected person, and the primary carer in consultation with the community mental health service. Under the 2007 revision of the *Act*, CTOs can be made whilst the patient is in the community, whereas previously this required an admission to a gazetted psychiatric hospital. Under the *Act* a CTO is made after application to either a magistrate or the Mental Health Review Tribunal for an inpatient. In the case of a patient in the community, the patient must receive a written notice of application for a CTO (s 52) including a ‘Treatment Plan’. The application must not be heard any earlier than 14 days after notice is given. A CTO can be made if person is absent from the hearing and proper notice has been given (s 55).

If a patient, subject to a CTO, is in breach of the conditions of the CTO (e.g. consistent non-attendance to appointments, an application can be made for a breach of CTO (S58)). This may result in the patient being taken to the community health centre or detained in a DMHF.

### Forensic Patients

A ‘forensic patient’ refers to a patient who has been convicted of a serious criminal offence and is released conditionally from a Corrective Services facility to care in the community. Such patient's care is provided by Area Mental Health Services and supervised closely by the Mental Health Review Tribunal. Based upon various clinical recommendations, the Mental Health Review Tribunal makes recommendations to the Minister for Health in regards to the ongoing care of such patients. Under the 2007 revision of the *Act*, such patient's care is now provided under the *Criminal Procedures Act*. At the time of writing, this legislation was undergoing parliamentary review.

**LEARNING OBJECTIVES**

- Outline the basic principles of the Commonwealth Privacy Act
- Describe the aspects of the Privacy Act in relation to healthcare

## The Commonwealth Privacy Act

### The Commonwealth Privacy Act 1998

The Commonwealth Government framed privacy legislation in 1998. This law was to be applied across a large number of settings in society. In 2001 this law was adapted to apply to the health care sector. This modification involved the framing of 10 “National Privacy Principles” in relation to the delivery of health care. Whilst these apply to the private sector and do not alter the effect of state Mental Health Legislation, the principles are still relevant to public sector psychiatry.

These principles are listed in Figure 1.

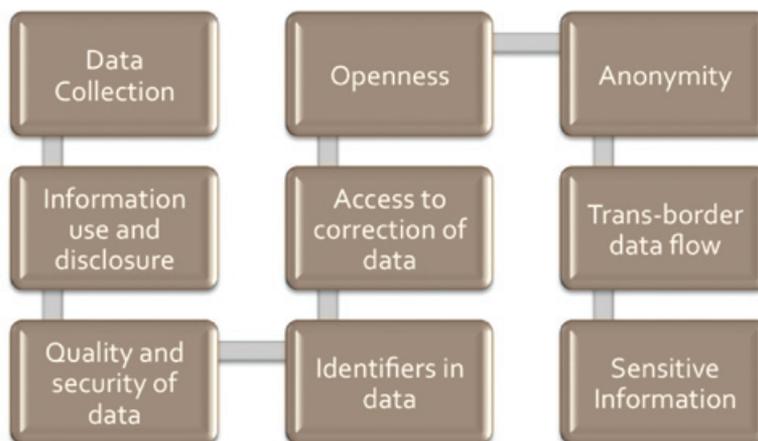


Figure 1 – The National Privacy Principles applied to healthcare

### *The 10 National Privacy Principles Applied to Healthcare*

#### ***NPP1: Collection of Information***

An organisation must not collect personal information unless the information is necessary health care. When the data is gathered, the person in question has to provided details of the organisation eg. Health Service or medical practice, and contact details. It is preferred the information be collected, where practical, from the patient themselves. If information is obtained from a third party, the patient must be made aware of this

#### ***NPP2: Use and Disclosure***

This principle outlines the use of information obtained about a patient. The primary purpose is for the benefit of the patient’s healthcare. Any secondary purpose eg. Research or epidemiological study must have the patient’s consent. Disclosure of information for marketing purposes must not include information of a sensitive nature. Breaches of this principle may occur in circumstances of public interest or the patient’s safety.

#### ***NPP3: Data Quality***

A health-care organisation must take reasonable steps to make sure that the personal information it collects, uses or discloses is accurate, complete and up to date.

#### ***NPP4: Data Security***

Sets standards for keeping information up-to-date, accurate and complete, as well as for protecting and securing it from loss, misuse and unauthorised access. This includes de-identification of transmitted data and security for electronic medical records.

#### ***NPP5: Openness***

This principle requires providers to be open about how they handle health information. Each organisation must develop a form of privacy policy to clearly explain to patients how it handles health information.

#### ***NPP6: Access and Correction***

This principle gives patients a general right of access to their own health records, and a right to have information corrected, if it is inaccurate, incomplete or out of date. Access to data can be reasonably refused if the request is frivolous, vexatious or may harm the patient's health. Access can also be refused if accessing the data may compromise a criminal investigation or may harm public interest. Any charges for accessing information must not be "excessive".

#### ***NPP7: Identifiers***

This principle limits the use of Commonwealth government identifiers, such as the Medicare number, Tax File Number or any Centrelink identifiers. Such data cannot be used outside of the institutional activities related to that identifier.

#### ***NPP8: Anonymity***

Where possible, patients must have the option of using health services without identifying themselves.

#### ***NPP9: Transborder data flows***

A health care organization can only transmit information relating to a patient outside of Australian Commonwealth jurisdiction if it is in the patient's best interest or, if related to a non-clinical purpose, it has the patient's consent. The jurisdiction receiving the information must have similar provisions for handling that information to the *Commonwealth Privacy Act*.

#### ***NPP10: Sensitive Information***

A healthcare organisation must not collect sensitive information about an individual unless the individual has consented; or the collection is required by law; or the collection is necessary to prevent or lessen a serious and imminent threat to the life or health of any individual. Any deviation from this principle relates to public interest or safety or the patient's interest.

### **LEARNING OBJECTIVES**

- Describe the basic provisions of the Guardianship Act
- Outline the role of the Office of the Protective Commissioner
- Understand the role of the psychiatrist in Guardianship proceedings

## **The Guardianship Act**

### **Introduction**

Whilst the *Mental Health Act* provides for involuntary detention and treatment of patients where a disturbance of mental health creates acute risk to self or the community, the *Guardianship Act* focuses on the welfare, interests and rights of the person with the disability and not public interest or safety. The *NSW Guardianship Act (1987)* exists to protect the interests and legal rights of people over the age of 16 years, who have a disability, such as severe mental illness or dementia that affects their capacity to make decisions. The principles of the *Guardianship Act* are listed in Table 1.

The *Guardianship Act* provides for the appointment of a guardian to make substitute decisions on behalf of an individual, where it is demonstrable that they have such impairment of judgement that they require additional support in making important personal decisions. The appointed guardian is either a private guardian, such as a family member, or the Public Guardian. The Public Guardian is usually appointed in situations where there is conflict, significant ethical considerations or where there is no other person able to take on the responsibility.

The appointed guardian takes on a role of making substitute decisions on personal issues such as accommodation, access to the patient, or consent to medical and dental treatment. Such decisions have the same legal status as if the patient had made the decision. In some circumstances, a guardian may give consent for the implementation of behavioural management strategies or restraint.

A guardian appointed by the Guardianship Board does not make decisions related to a patient's financial affairs. This responsibility is assumed by the NSW Trustee and Guardian (TAG) – affiliated with the Guardianship Board.

- The welfare of the person should be given paramount consideration
- The freedom of the person should be restricted as little as possible
- The person should as far as possible to live a normal life in the community
- The views of the person should be taken into consideration
- It is important to preserve family, cultural and linguistic environment of the person
- The person's autonomy should be encouraged as far as possible
- The person should be protected from abuse, neglect and exploitation
- The community should be encouraged to promote these principles.

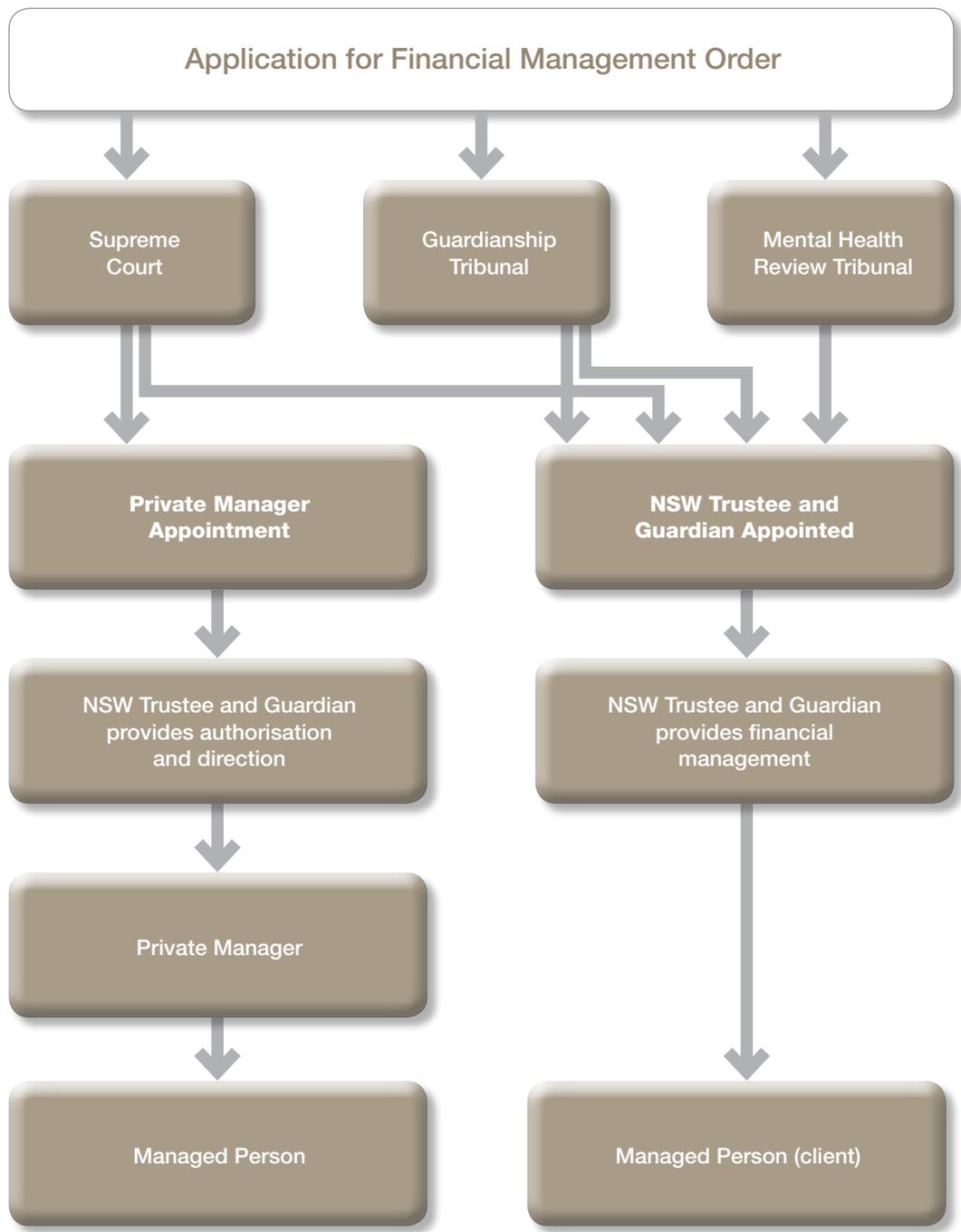
Table 1 – The principles of the *Guardianship Act* 1987

### The NSW Trustee and Guardian (TAG)

The TAG is required by law to make decisions that are in the best interests of the person whose financial affairs are under management. The Guardianship Tribunal will only make a financial management order if:

- The person is not capable of managing their affairs.
- There is a need for someone else to manage their affairs for them.
- It is in the person's best interests to have a financial management order.
- The person has assets in NSW.

If a patient's financial affairs are to be placed under the TAG a Financial Management Order (FMO) is made. Figure 1 shows the process of initiation of a Financial Management Order.



The domains of interest in a FMO are listed in Figure 2.

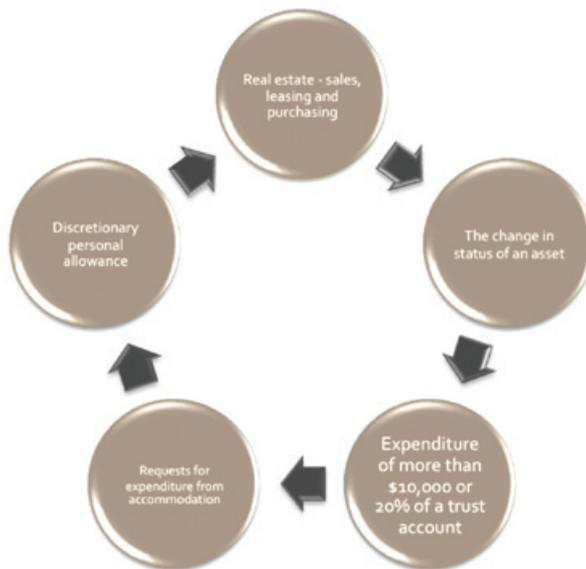


Figure 2 – Scope of FMO

### The role of psychiatrists in Guardianship or FMO

The primary legislative instrument in psychiatric practice is the *Mental Health Act*. In circumstances where the *Mental Health Act* applies, this in effect “trumps” the *Guardianship Act*. Psychiatrists do not usually make applications for FMO or guardianship on behalf of patients, however they are often requested to provide evidence to the Guardianship Board to inform its evaluation of applications. Such evidence usually addresses clinical issues such as the effect of a mental illness on a patient’s judgment or decision making capacity, any history of harm brought about by impaired judgment over affairs (e.g. Financial exploitation). Treatment decisions involving mental illness are usually considered in terms of the *Mental Health Act*.

#### LEARNING OBJECTIVES

- Define the concept of “capacity”
- Describe the different components to “capacity”

## Capacity as a legal construct in mental health care

### Introduction

The concept of capacity is at best elusive. This may in part be attributable to the different meanings of the term and its use. Like the concept of risk, no comprehensive or mutually agreed definition has been achieved and it remains situated in different discourses in law, medicine and society. The term capacity is polysemous and the multiple definitions relate to ability, efficacy or potential. Capacity is used synonymously with the term ‘competence’, although the latter also resides around abilities, particularly in relation to specific tasks. All participants acknowledged that the intrinsic impairments

arising from severe mental illness impacted upon capacity, and that any measure that sought to better such incapacity, either treatment, substituted or proxy decision-making, should enhance the person's abilities in responding to challenges.

In the North American literature, the concept of competency is not exclusively psychiatric but also resides in law and social settings<sup>132</sup>. In legal settings, capacity is task specific<sup>133</sup> and as far back as the 1940s it was acknowledged that mental illness itself does not present grounds to presume incompetence or incapacity<sup>134</sup>. In 1977 Roth and colleagues elaborated construct of competency, applied to the specific capacity to consent to psychiatric treatment. The components of this model included the capacity to evidence a choice, the reasonable outcome of such a choice, a choice based on rational reasons, the ability to understand treatment options, and demonstrating the actual understanding. None of these were a satisfactory or comprehensive account of capacity in treatment decisions.

Definitions of 'functional capacity' in the scientific literature involve the extent to which the person's understanding, knowledge, skills and abilities meet the demands involved in making a particular decision within a given context<sup>135</sup>. The problems with this construct are the fluid nature of some of the impairments, defining a threshold of impairment and distinguishing between conceptual and functional impairments<sup>135</sup>. The most authoritative empirical study of capacity in relation to treatment decisions was the MacArthur study, which sought to elaborate a clinical construct of competence to consent to treatment, using four 'sets of abilities' related to four legal standards<sup>136</sup>. These four abilities included:

- *Understanding treatment disclosures (UTD)* – encompassing the ability to paraphrase information, recall details and recognise elements of information about treatment
- *Perceptions of disorder (POD)* – was the capacity to both recognise the features of a disorder and acknowledge the benefits of treatment
- *Thinking rationally about treatment (TRAT)* – is the ability to make a decision about treatment and justify the decision
- *Expressing a choice (EC)* – described the ability to select and maintain a choice without ambivalence.

In an empirical study, the investigators compared subjects suffering from schizophrenia, depression and ischaemic heart disease. They demonstrated that subjects with depression and schizophrenia showed poorer understanding UTD, TRAT and POD, which was more pronounced in schizophrenia. These findings form the basis of the clinical assessment of competency to consent to medical or psychiatric treatment and are of critical importance to mental health legislation.

In the United Kingdom, there are more formal statutory definitions of incapacity. In British law, capacity is defined as a functional concept determined by 'the person's ability to understand, retain, and weigh up information relevant to the decision in order to arrive at a choice, and then a capacity to communicate that choice'<sup>137</sup>. The UK Law Commission defined incapacity as a person being unable by reason of 'mental disability' to make a decision of a matter in question. This arises from the inability to understand relevant information and make a decision based on that information<sup>138</sup>.

<sup>132</sup> Shah S. Dangerousness and civil commitment of the mentally ill: some public policy considerations. *American Journal of Psychiatry*. 1975;132:501-505.

<sup>133</sup> Hardisty J. Mental Illness: a legal fiction. *Washington Law Review*. 1973;48:735062.

<sup>134</sup> Grisso T. *Evaluating Competencies: Forensic Assessments and Instruments*. New York: Plenum Press; 1986.

<sup>135</sup> Roth L, Meisel A, Lidz C. Tests of competency and consent to treatment. *American Journal of Psychiatry*. 1977;134:279-284.

<sup>136</sup> Grisso T, Appelbaum P. The MacArthur Treatment Competence Study. III : Abilities of patients to consent to psychiatric and medical treatments. *Law and Human Behaviour*. 1995;19:149-174.

Appelbaum P, Grisso T. The MacArthur Treatment Competence Study, I: Mental illness and competence to consent to treatment. *Law and Human Behaviour*. 1995;19:105-126.

Grisso T, Appelbaum P, Mulvey E, Fletcher K. The MacArthur Competence Study, II: Measures of abilities related to competence and consent to treatment. *Law and Human Behaviour*. 1995;19:127-148.

<sup>137</sup> Wong J, Clare I, Gunn M, Holland A. Capacity to make health care decisions: its importance in clinical practice. *Psychological Medicine*. 1999;29:437-446.

<sup>138</sup> UK Law Commission. *Mental Incapacity: A Summary of the Law Commission's Recommendations (LC231)* Stationery Office. London; 1995.

The UK's *Mental Capacity Act* (2005) links incapacity to the presence of an impairment of a disturbance in the functioning of the mind, leading to inabilities in the realm of:

- 1) Understanding the information relevant to a decision
- 2) Retaining the information
- 3) Utilising the information as part of the process of making decisions, and
- 4) Communicating the decision.

In the UK an adult is presumed to have capacity to withhold consent unless demonstrated otherwise and that presumption can be rebutted based upon difficulties involving thought, affect and cognition associated with serious psychiatric and intellectual disabilities. Despite the clarity of the legal definitions, there are many conceptual and practical problems with this approach<sup>8</sup>. In clinical settings, the proposed means to improve capacity include attention to communication problems, improving how information is provided, ameliorating the effects of a mental disability, addressing the patient's sometimes inherent pessimism, avoiding coercion and acknowledging religious, cultural or spiritual beliefs<sup>139</sup>. Under law, the courts seek to address incapacity by considering advance directives, proxy decision-making or substituted judgement. The latter is based upon speculation of the nature of the decisions likely to be made by the person if competent and utilises a 'best interests' test.

There are no uniform Commonwealth laws in relation to capacity in Australia, not least because under the Constitution this is principally a matter for State and Territory law. In Queensland the *Guardianship and Administration Act* (2000) defines capacity under a 'decision-specific' approach. Schedule 3 of the Queensland Powers of Attorney Act (2003) defines capacity in terms of understanding the nature of decisions about a particular matter, freely and voluntarily making decisions about the matter and communicating the decision<sup>140</sup>.

By contrast, in NSW there is no single definition of capacity, but rather it resides in a number of common law or statute definitions. The NSW Department of Attorney General and Justice published a 'Capacity Toolkit' for legal practitioners in relation to decisions around medical treatment, lifestyle and finance averring the general principle of establishing that the person understood the facts, understood the main choices that exist, evaluate and compare the consequences and understand the effect of these<sup>141</sup>. In 2006 the then Department of Ageing, Disability and Homecare formulated a policy defining capacity:

'Capacity is subject to fluctuations and is influenced by the internal and external environment of the individual. Ultimately, individuals must be able to understand the information relating to decisions they are required to make, and the effects of those decisions<sup>142</sup>.'

As yet, there are no comprehensive tests of capacity in the setting of mental health law in NSW.

<sup>139</sup> Bellhouse J, Holland A, Clare I, Gunn M. Decision-making capacity in adults: its assessment in clinical practice. *Advances in Psychiatric Treatment*. 2001;7:294-301.

<sup>140</sup> Victorian Law Reform Commission. *Guardianship: Final Report*. Melbourne; 2011.

<sup>141</sup> NSW Government. Capacity Toolkit. In: Department AGs, ed. Sydney: NSW Government; 2008.

<sup>142</sup> Disability Council of NSW. Are the rights of people whose capacity is in question being adequately promoted and protected? Sydney: Submission to the NSW Attorney General's Department; 2006.







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