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REVIEW ARTICLE

Monitoring for antidepressant-associated adverse events in the treatment of patients with major depressive disorder: An international consensus statement

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ABSTRACT

Objectives: These recommendations were designed to ensure safety for patients with major depressive disorder (MDD) and to aid monitoring and management of adverse effects during treatment with approved antidepressant medications. The recommendations aim to inform prescribers about both the risks associated with these treatments and approaches for mitigating such risks.

Methods: Expert contributors were sought internationally by contacting representatives of key stakeholder professional societies in the treatment of MDD (ASBDD, CANMAT, WFSBP and ISAD). The manuscript was drafted through iterative editing to ensure consensus.

Results: Adequate risk assessment prior to commencing pharmacotherapy, and safety monitoring during pharmacotherapy are essential to mitigate adverse events, optimise the benefits of treatment, and detect and assess adverse events when they occur. Risk factors for pharmacotherapy vary with individual patient characteristics and medication regimens. Risk factors for each patient need to be carefully assessed prior to initiating pharmacotherapy, and appropriate individualised treatment choices need to be selected. Some antidepressants are associated with specific safety concerns which were addressed.

Conclusions: Risks of adverse outcomes with antidepressant treatment can be managed through appropriate assessment and monitoring to improve the risk benefit ratio and improve clinical outcomes.

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1. Introduction

Antidepressants are the fourth most commonly prescribed category of pharmaceuticals in Organisation for Economic Co-operation and Development (OECD) countries (OECD 2013), with a rising trajectory (Stuart et al. 2017). Antidepressant exposure is associated with some risk of adverse outcomes that range in both severity and prevalence. Common adverse events include headache, nausea, agitation, sedation, sexual dysfunction, diminished mental acuity and memory, weight gain and metabolic abnormalities (Anderson et al. 2012). Rarer and more serious adverse events include cardiac (Dziukas and Vohra 1991; Jasiak and

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Bostwick 2014), neurological (including seizures) and hepatic (Carvajal Garcia-Pando et al. 2002) side effects, as well as putative risks such as increased suicidality in youth (Culpepper et al. 2004). Beyond subjective discomfort and medical comorbidities, adverse effects are a major reason for treatment discontinuation (Keitner 2010), which in turn increases the likelihood of poor treatment outcomes. Thus, managing adverse events associated with antidepressant use is an important issue for both patient safety and enhancing real world effectiveness. In this context, it is important to note that untreated mental illness itself presents with a myriad of risks and adverse outcomes, and the risks of not receiving treatment are often under recognised (Berk and Parker 2009).

An international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP) has developed practice guidelines for the biological treatment of unipolar depressive disorders (Bauer et al. 2002a; Bauer et al. 2002b; Bauer et al. 2007; Bauer et al. 2013; Bauer et al. 2015). The Canadian Network for Mood and Anxiety Treatments (CANMAT) has produced clinical guidelines for the management of patients with major depressive disorder (MDD), and these guidelines include recommendations concerning patient safety (Kennedy et al. 2016; Lam et al. 2016). Medication recommendations for MDD have also been recently produced that document the consensus recommendations of a Florida Expert Panel and include safety recommendations (McIntyre et al. 2017). Regional safety guidelines for antidepressant use have also been published for Australian practitioners (Dodd et al. 2011). We believe that there is a need for new consensus recommendations that specifically address issues of antidepressant treatment safety, have a broader international consensus and update previous guidelines.

These recommendations reflect an expert consensus on the assessment and monitoring of patients prior to commencing and during pharmacotherapy for MDD. These recommendations are presented in a user-friendly format as a practical guide for clinicians. All co-authors approved the final version of the recommendations which have also been endorsed by WFSBP, CANMAT, the Australasian Society for Bipolar and Depressive Disorders (ASBDD) and the International Society for Affective Disorders (ISAD).

2. Method

An intention to publish up-to-date, international consensus safety recommendations for antidepressant use in the treatment of MDD was catalysed among researchers who are members of ASBDD and CANMAT, with both organisations officially backing this project. WFSBP and ISAD were approached to participate and co-authors were nominated from all participating organisations. Authors were selected based on their expertise, experience, membership of a participating society, and willingness to participate. The scope of these consensus recommendations was limited to safety concerns for medications that are primary antidepressant therapies for MDD. Augmentation agents, off-label medications and medications primarily used for other indications, were considered out of scope. From November 2015 to January 2016, multiple comprehensive computer-aided searches of peer-reviewed literature were performed without date limits. Pubmed, OVID, Medline and reference lists of relevant publications were searched. Data searches were conducted on multiple occasions by individual co-authors at later dates up to November 2016. Recommendations were drafted and circulated for editing and contribution from co-authors iteratively until all co-authors approved the final version. Approval from ASBDD, CANMAT, WFSBP and ISAD was requested to associate these consensus recommendations with these societies.

The recommendations are arranged in sections; assessment (Section 3), monitoring (Section 4), special populations (Section 5), managing adverse events (Section 6) and management of overdose (Section 7). Some safety concerns occur in more than one section (e.g., hepatic function) and efforts have been made to avoid repetition. A summary of recommendations of safety monitoring for antidepressant treatment is given as Table 1.

3. Consensus recommendations for the administration of antidepressants

3.1. Evaluating whether a treatment for MDD should be commenced or continued

For each new patient suffering from MDD, the decision to prescribe an antidepressant – or not – needs to be evaluated as part of a collaborative approach to the therapeutic alliance (Berk et al. 2004). Treatment should be commenced or continued if the patient agrees with the treatment plan and regimen, accepts its risks and benefits, and the treating physician considers the benefits of treatment to outweigh the risks. Careful assessment should be made on an individualised basis.

A diagnostic work up should be conducted prior to making any diagnosis or treatment decisions to ensure that potentially relevant or complicating medical or

Table 1. Summary of recommendations of safety monitoring for antidepressant treatment.

	Recommendation
Baseline assessments	Highly recommended • Diagnostic work up/differential diagnosis including considering organic causes of depression • Personal and family history including previous antidepressant use • Physical health, including body mass index and (whenever deemed appropriate) waist circumference; metabolic syndrome; sexual health/dysfunction; hypertension; alcohol, tobacco and substance use and dependence Also to be considered • Pregnancy test • Liver function test (required for agomelatine) May be considered • Electrocardiogram for pre-existing cardiovascular disease • Bone density scan, esp. when risk factors for osteoporosis are present • Electrolytes, esp. in older patients
Assessments during treatment	Check for change compared to baseline • Weight and (whenever deemed appropriate) waist circumference • Sexual dysfunction Check for treatment-emergent adverse effects • Suicidal thinking, esp. in young people • Increased serum transaminase (LFT required for agomelatine) • Hyponatraemia, esp. in older people • Hypertension; orthostatic hypotension
Special populations	Special considerations are required for children, the elderly, women during reproductive events, and people with concurrent mental and physical disorders

psychiatric conditions are addressed. A decision to treat or not to treat should then be discussed with the patient, as well as discussing the full range of treatment options including psychosocial treatments, if appropriate. Assessments presented in Section 3.3 of this review may be useful for improving diagnostic clarity.

3.2. Choice of treatment

Choice of treatment is made based on a number of factors including efficacy and tolerability of individual antidepressants, past history of response and tolerance, the person's clinical symptom profile, personal preferences and cost. Antidepressant combinations, augmentation strategies and other medication options and somatic therapies are typically reserved for those who have not responded to antidepressant monotherapy (Dodd et al. 2005) and are beyond the scope of these recommendations. These recommendations do not address head-to-head comparisons of safety and tolerability for individual treatment options. Rather, they are intended to provide guidance on patient and medication-related factors that should be taken into account when evaluating safety and tolerability of a treatment choice.

3.3. Pre-treatment assessment

The baseline assessment includes information on the clinical state prior to treatment initiation and should therefore establish baseline parameters for monitoring safety and tolerability during treatment. Data regarding the nature and course of the disorder, detailed clinical histories, differential diagnoses, medical and psychiatric comorbidities, past history and family history of treatment response/non-response and tolerability are necessary to inform treatment choice, which also needs to be tailored to personal preference, as well as cultural and environmental factors.

3.3.1. Scales and assessment prior to or during the patient interview

Self-rated questionnaires may be used in the waiting room or online to assist in collecting details such as medical and family history. Using symptom scales, patient and family history questionnaires, and screening tools may facilitate data collection and may be practicable in many practice settings. There are no recommended specific mental health instruments; however, some health services may mandate the use of particular questionnaires and scales.

Comprehensive structured diagnostic interview scales are also available to identify comorbid psychiatric disorders, although these tend to be time-consuming and are generally reserved for research purposes. Comorbid substance use disorders should be treated or referred to specialist care, depending on local protocols. Other medications currently being used by the patient should be documented and risks of drug–drug interactions assessed.

3.3.2. Laboratory tests

Most national and international guidelines address laboratory tests before and during antidepressant treatment.

Their inclusion in these current international recommendations is contentious as tests may be unnecessary, are not necessarily cost effective, and may unnecessarily raise the cost of treatment. Some tests are mandated by regulatory authorities in nations or regions where those regulatory authorities have jurisdiction. Currently, the only baseline laboratory tests mandated by health regulatory agencies are liver function tests prior to, during and after discontinuation of treatment with agomelatine and nefazodone. The regulations with regard to agomelatine were initiated by the European Medicines Agency (EMA), including that this should not be initiated, or treatment should be discontinued, if serum transaminase levels are higher than three times the upper limit of the normal range (European Medicines Agency 2008). Proprietary nefazodone was discontinued in 2003 because of hepatic adverse events, although some generic formulations remain available in some markets. Elsewhere, other regulatory authorities have approved product information provided by the pharmaceutical companies which includes the EMA testing requirements.

There are divergent views regarding the routine use of baseline laboratory testing which reflects the limitations in the evidence and different standards across individual countries. For example, CANMAT guidelines advise against routine laboratory testing, including therapeutic drug monitoring and genetic and CYP450 analyses, and recommend such testing only when clinically indicated. In contrast, some countries have guidelines and regulations where some tests, such as liver function tests for patients treated with agomelatine, are mandatory. Consequently, these international consensus recommendations describe what tests are available without making recommendations for use of a specific test. Further research efforts are in progress and recommendations may change as new data emerge.

In clinical practice, most clinicians do not routinely order laboratory tests before and after antidepressant treatment. On the other hand, laboratory tests can be useful to determine baseline measurements prior to commencing treatment, determine risk factors and to exclude physical illnesses contributing to depressive symptoms. The decision to request tests may be influenced by local regulations, availability and cost of testing. Decisions may also be made on a case-by-case basis determined by risk and personal preference.

3.3.2.1. Tests to rule out medical diagnoses in the differential diagnosis of MDD. *Complete Blood Cell count:* A complete blood cell count is useful to assess whether depressive symptoms are related to anaemia and its causes, including B12 or folate deficiency, or systemic inflammation detected by an elevated white blood cell count.

Thyroid function: Hypothyroidism (and to a lesser extent hyperthyroidism) can be associated with symptoms including emotional lability, cognitive impairment, fatigue and lethargy that may be misdiagnosed as MDD (Bauer et al. 2008). In many settings, a thyroid-stimulating hormone (TSH) level is considered to be an adequate screen for detecting subclinical or incipient hypothyroidism. Two large cohort studies of outpatients with depression ($N = 235$, Iosifescu et al. 2001; and $N = 200$, Fava et al. 1995) have shown that hypothyroidism and hyperthyroidism are uncommon, with no clinical cases in either study, and that the presence of subtle thyroid function abnormalities does not appear to have an impact on treatment outcome (Fava et al. 1995; Iosifescu et al. 2001). Where abnormal thyroid function is detected in patients with depression, TSH and thyroid hormone levels (T3 and T4) should be normalised. If the physician is not familiar with correcting thyroid hormone levels, patients should be referred to an endocrinologist or internist. Depressive symptoms may resolve when abnormal thyroid hormone levels are corrected. In a subgroup of patients, additional treatment of depressive symptoms with an antidepressant (any class) may be required. It should be noted that thyroid dysfunction has been associated with treatment non-response, even if corrected (Berlin et al. 1999; Dodd and Berk 2004).

Screen for alcohol and substance abuse and dependence: Alcohol and substance abuse and dependence are a common co-morbidity with MDD. Their detection is important not only for clinical treatment, but also for safety concerns with pharmacotherapy. Diagnostic clarity can be confounded by covert substance use, with intoxication or substance withdrawal, especially psychostimulant withdrawal, being confused for mood symptoms (Barr et al. 2002). Pharmacodynamic and pharmacokinetic drug–drug interactions with alcohol, tobacco and illicit substances are a significant risk (Dodd et al. 2011). It is reasonable to enquire about use on a regular basis, even if the criteria for dependence or abuse have not been met. Alcohol- (Menkes and Herxheimer 2014) and tobacco (Nemeroff et al. 1996)-associated risks are well documented. Less is known about interactions between antidepressants and illicit drugs, where case reports have demonstrated potentially serious risks (Silins et al. 2007). Blood, saliva or urine screening for substance use, and breath testing for alcohol or exhaled carbon monoxide can only detect substances present at the time

of testing. Information gathered from family, friends and other health professionals may be more reliable and assist in providing an understanding of an individual's substance and alcohol use. As with illicit substances, some prescription drugs may cause or aggravate depressive symptoms and may produce drug–drug interactions (Dodd et al. 2011). Using self-report scales including the Drug Abuse Screening Test (Gavin et al. 1989) and the Michigan Alcohol Screening Test (Selzer 1971) may have advantages compared to laboratory testing, such as lower costs, greater sensitivity and benefits for the therapeutic alliance.

Screening for infectious diseases: Infectious diseases may occasionally cause symptoms that overlap with MDD, including somatic symptoms, fatigue, malaise, aches and pain (Maes 2009). These symptoms may persist after the acute infection has resolved (Nolan et al. 2012). Viral and other infections can be screened for using blood samples. Symptoms of infection, such as fatigue and anhedonia, may overlap with symptoms of depression. Some viral infections have also been associated with a higher incidence of MDD, including human immunodeficiency virus (HIV) (Shacham et al. 2009), hepatitis C (Bailey et al. 2009), West Nile virus (Murray et al. 2007) and Epstein-Barr virus (Miller et al. 1986; Miller et al. 2005). Erythrocyte sedimentation rate and C-reactive protein levels may be informative where an infection is suspected, although these tests are relatively non-specific. Depressive symptoms have been reported as the most common side effect of interferon treatment for hepatitis C, and pre-treatment with SSRIs may prevent depressive symptoms associated with interferon treatment (Lucaciu and Dumitrascu 2015).

A 24-h urinary free cortisol test: This can detect hyper- and hypocortisolaemia, which may each manifest with depressive symptoms (Wolkowitz et al. 2009). Depressive symptoms associated with Cushing's syndrome may resolve with treatment of the endocrine disorder (Wolkowitz et al. 2009). Endocrine disorders are discussed in greater detail in Section 5.3.4 of this review.

Neuroimaging and cognitive neuropsychological testing: For late onset MDD, MRI may be useful for determining if small vessel disease is an underlying cause (O'Brien et al. 1998). Cognitive neuropsychological testing can identify cognitive impairment. MDD is associated with broad impairment in multiple aspects of executive function and memory (Wright and Persad 2007; Snyder 2013; Keefe et al. 2014). MRI and cognitive neuropsychological testing may also provide a useful baseline measure for future assessments, particularly as late onset MDD has been identified as a risk factor for dementia (Kohler et al. 2015).

3.3.2.2. Tests to assess baseline functioning for factors that can be affected by antidepressants. *Body mass:* Major depressive disorder and antidepressant treatment are both associated with weight changes. Weight changes are a common and serious concern for people being treated with some antidepressants and are associated with many comorbid physical illnesses (Fava 2000). Increased weight may also be a precursor to development of the metabolic syndrome (Heiskanen 2015). Weight and waist circumference should be measured and recorded prior to commencing treatment with an antidepressant. The non-unanimous but majority consensus view of the author group was that indices of the metabolic syndrome including lipids, blood pressure and glucose should be measured if indicated.

Sexual health: Treatment-emergent sexual dysfunction is a common adverse effect of antidepressant treatment with data to suggest that 27–65% of female and 26–57% of male patients experience either a worsening of pre-existing difficulties or treatment-emergent difficulties in the early stages of treatment (Baldwin et al. 2013). However, this not infrequently occurs on top of an already significant pre-treatment level of sexual dysfunction, with one study finding sexual problems of some type were found in 26% of subjects without a mental illness, 45% of non-treated depressed patients and 63% of treated depressed patients (Angst 1998). Validated scales should be used to assess sexual health: examples are the Arizona Sexual Experiences Scale (ASEX), the Sexual Functioning Inventory (SFI), Changes in Sexual Functioning Questionnaire (CSFQ), the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX), and the Sex Effects Scale.

Cardiac safety: Blood pressure and pulse should also be checked, as some agents affect blood pressure; pre-existing hypertension is a risk factor for cardiovascular adverse reactions (Spindelegger et al. 2014).

Pregnancy test: Pregnancy status should be clarified before commencing an antidepressant in all women of reproductive age, and formal pregnancy testing may be indicated if there is uncertainty. Pregnancy is associated with foetal exposure to some antidepressants and their metabolites and hence teratogenicity, and there are also potential risks associated with pharmacokinetic changes for some agents. Pharmacological management of MDD therefore needs to vary substantially in accordance with reproductive status (Deligiannidis et al. 2014).

Liver function tests (LFTs): The elderly, people with comorbid substance use disorder and people taking multiple medications are considered high-risk groups for impaired liver function. Hepatitis C has been associated with depressive symptoms, independent of treatment with interferon-α, and substance or alcohol abuse (Carta et al. 2007). Transaminase levels and other indicators of liver injury are recommended in cases where there is a clinical index of suspicion regarding risks for hepatic dysfunction such as comorbid alcohol abuse. Where abnormal LFT findings are observed at baseline, the cause of the abnormal findings should be investigated and, if the level of liver injury is worrisome, initiating antidepressant treatment may need to be delayed until the problem is clarified. If baseline liver tests are outside of the normal range and if clinically indicated, (e.g., at least twice the upper limit of normal), agents with a lower risk of hepatic dysfunction should be chosen. In such instances, treatment can be initiated with an antidepressant, weighing risks and benefits, and ongoing liver monitoring is recommended. Generally, these blood tests are reviewed yearly unless there is cause to look at them more frequently. Recommendations on the management of patients with antidepressant-induced liver injury are presented in Section 6 of this review. Management of patients with pre-existing hepatic disease is discussed in Section 5.3.1, and liver dysfunction as an adverse drug event in Section 6.1.

Pharmacogenetic testing: This is available for a large and growing list of genes associated with pharmacokinetic and pharmacodynamic variations (Singh and Bousman 2017). Testing for gene variants in CYP2D6 and CYP2C19 enzymes to determine metaboliser status are the most evidence-based pharmacogenetics tests relevant to antidepressant treatment (Muller et al. 2013). There is some evidence to suggest potential usefulness of such testing in some select cases (Brennan et al. 2015), though not sufficient to justify widespread clinical use. The International Society for Psychiatric Genetics does not recommended genetic testing for patients using antidepressants (International Society of Psychiatric Genetics 2016). Further evidence is required to clarify if these tools are clinically useful and cost effective (Bousman and Hopwood 2016).

Electrocardiogram (ECG): This can be used to detect problems with cardiovascular conduction and to establish a baseline measure of cardiac functioning prior to commencing antidepressant treatment. Electrocardiographic changes have been reported for tricyclic antidepressants (TCA), SSRIs, SNRIs, mirtazapine and bupropion, especially in the elderly and at high doses (Goldberg and Ernst 2012). Baseline ECG measurements are recommended for patients with pre-existing cardiovascular disorders (Dodd et al. 2011).

Bone density scan: There is epidemiological evidence suggesting an association between serotonergic antidepressant use and changes in bone mineral density. This has been linked to evidence that serotonergic agents influence osteoblast and osteoclast development and bone formation (Williams et al. 2008; Hodge et al. 2013), although the clinical significance of these findings is still under investigation. Baseline bone density scans in those at high risk for osteoporosis may be useful for monitoring bone changes after long-term administration. It should be noted that not only is antidepressant use a risk factor for osteoporosis, but MDD itself is also a risk (Fernandes et al. 2016). In addition, many of the known risk factors for MDD also increase risk for osteoporosis, including physical inactivity, poor diet and smoking. Heel ultrasound, as a measure of bone quality, has been proposed as a lower-risk screening tool being devoid of the risks of ionising radiation, although its use as well as that of that of dual-energy X-ray absorptiometry scanning requires further clarification (Williams et al. 2013; Rauma et al. 2015). Bone health is discussed in greater detail in Section 5.3.2 of this review.

4. Ongoing treatment monitoring

Weight and (whenever possible) waist circumference change from baseline should be recorded at scheduled visits. Indices of the metabolic syndrome should be monitored if indicated. Sexual health adverse effects should similarly be questioned at scheduled visits, and assessed using a validated scale if indicated.

Initiation of antidepressant treatment has been associated with possible increased risks of suicidal thinking and behaviour in young people aged 18–24 years during initial treatment (generally the first 1–2 months) (Hammad et al. 2006). These findings triggered an FDA black box warning and a consequent decrease in SSRI prescriptions, decrease that was associated with increases in suicide rates in children and adolescents (Gibbons et al. 2007; Friedman 2014). More recently, research has failed to demonstrate a clear increased risk of suicide in young patients prescribed antidepressants (Gibbons et al. 2012). However, a recent meta-analysis of 12 clinical trials of antidepressant versus placebo (all ages) demonstrated a higher incidence of suicidal events in antidepressant treated study participants compared to placebo-treated study participants (Baldessarini et al. 2017).

Further research is needed to full estimate any risks. Although the benefit of treatment now appears to exceed the suicide risk, monitoring for suicide risk in young people treated with antidepressants remains warranted in the acute phase of MDD and the first month of remission at a minimum.

Blood parameters may be checked during treatment. Liver function testing is mandated by some regulatory authorities for agomelatine in the countries where it has been registered. These mandatory requirements are for liver function testing conducted at baseline and around 3, 6, 12 and 24 weeks from initiating treatment or when dose is increased, and thereafter when clinically indicated (Servier Laboratories 2014). The testing schedule mandated by regulators may be followed by clinicians outside of the jurisdiction of these regulators, or for other antidepressants, if desired. Agomelatine and nefazodone treatment should be discontinued immediately if LFT measurements show serum transaminase concentrations greater than three times the upper limit of normal or if signs or symptoms of potential liver injury are observed. No data are available on the safety of agomelatine rechallenge after abnormal LFT measurements have resolved. Consequently, rechallenge is not advised.

Monitoring of cardiac function including blood pressure may be advised if a monoamine oxidase inhibitor (MAOI) or a TCA or high doses of citalopram (Castro et al. 2013) are prescribed or for people who have risk factors for cardiovascular disease, including the metabolic syndrome, smokers and people with a previous or family history of cardiovascular disease. Pre-existing cardiovascular disease is discussed in greater detail in Section 5.3.3 of this review. Cardiac safety in overdose is discussed in Section 7 of this review. Blood pressure changes associated with the initiation of treatment are known for some antidepressant agents, including hypertension with both venlafaxine and desvenlafaxine treatment (Thase et al. 2015) and orthostatic hypotension with phenelzine, tranylcypromine and the tetracyclic antidepressants (Moller et al. 1983).

4.1. Other 'at risk' monitoring

Hyponatraemia risk should be monitored in at risk groups. SSRIs and SNRIs, especially sertraline and escitalopram, have been associated with hyponatraemia, although this is also documented for other agents such as mirtazapine (Jung et al. 2011). The risk of hyponatraemia is significant in older patients and increased in females (Giorlando et al. 2013). SSRIs and SNRIs may have a greater risk for hyponatraemia compared to other antidepressants (Giorlando et al. 2013). There is evidence to suggest that hyponatraemia is not dose dependent (Giorlando et al. 2013). When deemed clinically appropriate, electrolyte assessment should be conducted at baseline for elderly patients prior to initiating treatment with an SSRI or an SNRI. In these patients, electrolytes should be assessed at baseline and in the first 3–5 weeks following initiation of antidepressant treatment or if symptoms of hyponatraemia (nausea, vomiting, headache, confusion, fatigue, muscle weakness) are suspected.

Therapeutic drug monitoring (TDM) of antidepressants can be used to measure drug and metabolite concentrations in body fluids (Hiemke 2008). Although TDM of antidepressants may have some utility for guiding therapy with TCA administration, it is of limited use as a safety screen. Rather than the regular measurements conducted with TDM, measurement of drug and metabolite concentrations in a single biofluid specimen may also be considered when there are reasons to suspect unusual concentrations. TDM may be expensive or unavailable or of insufficient quality. Where TDM demonstrates an excessively high or low plasma concentration of an antidepressant, further investigations may be required to uncover the cause. Non-adherence is the most common cause of low antidepressant plasma concentrations and TDM can be thwarted by patients who take their medications on the days prior to TDM.

Rare adverse events, such as blood dyscrasias (Levin and DeVane 1992), have been reported with antidepressant use. These idiosyncratic events are too uncommon to justify monitoring; however, treating clinicians should be vigilant about their symptoms. They are not dose related.

5. Special populations

5.1. Children

Antidepressant use in children is controversial due to concerns about safety, tolerability and efficacy, as well as a paucity of evidence from high-quality clinical trials (Jureidini et al. 2004). Antidepressant doses for use in children should be age and weight appropriate, and agents with better tolerability profiles should be selected as first line therapies. Antidepressant use in children is controversial and psychological therapies are usually preferred. A US FDA boxed warning of increased suicidal thoughts and ideation in children and adolescents is still current.

5.2. Pregnancy and breastfeeding

All antidepressants can cross the placenta and can cross into breast milk, exposing the foetus and the breastfeeding infant to antidepressants used to treat the mother. Safety concerns vary with stage of pregnancy and with choice of antidepressant agent. Antidepressant treatment guidelines for pregnancy and breastfeeding exist elsewhere (Dodd et al. 2000a; Kennedy et al. 2009; Lam et al. 2009; Yonkers et al. 2009; Beyondblue 2011; Bauer et al. 2013; National Institute for Health Care and Excellence 2014) and are beyond the scope of this article. Generally, the advantages of treating depression outweigh risks to the foetus or the breastfeeding infant. Risks can be minimised by following guidelines.

TDM of maternal plasma and breast milk can be performed but is generally not necessary. Measuring antidepressant concentrations from heel prick blood specimens in infants is not recommended, as it is stressful for mothers and infants, and antidepressant levels in infant blood are almost always present at levels below the limit of detection of most routine analytical methods (Dodd et al. 2000b).

Maternity and child health services should be informed if a patient is taking antidepressant medications and may have their own protocols for this situation. Antidepressant use alone is not generally sufficient to warrant classifying a pregnancy as 'high risk'.

5.3. The elderly

Elderly people with MDD are more likely to have concurrent physical illnesses and may already be taking medications for physical illnesses, which need to be considered when prescribing an antidepressant. Renal and hepatic function may be decreased and may need to be investigated before commencing treatment. Patients should be administered antidepressants at an age-appropriate dose and be carefully monitored for adverse effects. Lower doses are recommended due to increased end organ sensitivity and decreased tolerability (Cleare et al. 2015).

Studies of SSRIs, TCAs, monoamine oxidase inhibitors (MAOIs) and newer antidepressants in elderly people have demonstrated different risk profiles, but there is no clear evidence that any drug class is associated with reduced risks in an elderly population (Coupland et al. 2011). Newer antidepressants and SSRIs, considered to be a safer option in adult populations, may be associated with increased risk in the elderly of hyponatraemia (Coupland et al. 2011). Antidepressant-induced delirium is also more likely in an elderly patient (Kogoj 2014). Antidepressants associated with orthostatic hypotension or sedation should be avoided in elderly people as they may cause falls (Williams et al. 2015). There are inconclusive data to support the use of antidepressants for elderly patients with dementia (Leong 2014).

5.4. Concurrent medical disorders

In people with concurrent general medical conditions, there are conflicting data regarding recognition of MDD (Menear et al. 2015b) and adequacy of treatment (Menear et al. 2015a). Physically ill patients are generally excluded from large clinical trials of antidepressants, resulting in a paucity of efficacy and safety data in this population. Some clinical trials of antidepressants for individuals with specific comorbid illnesses have been conducted. These include chronic heart failure (O'Connor et al. 2010), where sertraline was not superior to placebo despite previous evidence of efficacy of SSRIs for treating MDD with comorbid ischaemic heart disease (Rivelli and Jiang 2007), Parkinson's disease where SSRIs and SNRIs have been shown to be effective and well tolerated for comorbid MDD (Richard et al. 2012) and Alzheimer's disease, where mirtazapine and sertraline were not superior to placebo (Banerjee et al. 2012). A study of patients with HIV treated with SSRIs reported reduced bone mineral density(Mazzoglio y Nabar et al. 2015), though it is unclear whether this was due to the SSRI treatment, HIV itself or a effects of antiretroviral treatment (Kruger and Nell 2017). Antidepressant safety concerns in bone mineral density in people living with HIV include balancing the risks and benefits of treatment. Nonetheless, there are sufficient data to suggest that many physically ill people with MDD may benefit from antidepressants (Ramasubbu et al. 2012).

5.4.1. Hepatic and renal dysfunction

Hepatic and renal dysfunction raise challenges for pharmacotherapeutic management of MDD. Dose reduction may be required in some circumstances. In a trial of citalopram, dose reduction was not warranted for people with moderate renal insufficiency but may be necessary for impaired hepatic function or severe renal insufficiency (Joffe et al. 1998). The need for dose reduction will depend on the percentage of renal or hepatic clearance of a drug and active metabolites, which varies between antidepressant agents, as well as the severity of renal or hepatic dysfunction. Where renal or hepatic dysfunction is known or

suspected, the extent of dysfunction will need to be determined.

5.4.2. Bone health

There is a paucity of knowledge about the effects of antidepressant treatment on pre-existing low bone density or osteoporosis (Williams et al. 2016). Agents with a lower propensity for inhibiting bone cell function may be considered. Differences between SSRIs in vitro in bone cell cultures suggested sertraline > fluoxetine > paroxetine > fluvoxamine > citalopram for inhibiting bone formation and function (Hodge et al. 2013); however, these laboratory experiments provide a low level of clinical evidence, so the clinical significance between agents with regards to human bone health is not fully known. Reduced bone mineral density and bone loss over time has also been established for TCAs and other classes of antidepressants (Rauma et al. 2016).

5.4.3. Cardiovascular disease

In patients with pre-existing heart disease, TCAs were commonly used prior to the development of newer generation antidepressants (Veith et al. 1982). However, they can cause prolongation of the QTc segment (Vieweg and Wood 2004) and atrioventricular block is increased in patients with pre-existing bundle branch block (Roose et al. 1987). MAOIs are commonly associated with hypotension and tachycardia (Yekehtaz et al. 2013), and rare cases of hypertensive crisis (Lavin et al. 1993), and so are not generally advised for patients with cardiovascular disease (CVD; Teply et al. 2016). SSRIs and SNRIs have better cardiac safety profiles and are more appropriate for use in patients with pre-existing CVD; nevertheless there are case reports of orthostatic hypotension, mild bradycardia, and conduction abnormalities with SSRI use, and both venlafaxine and desvenlafaxine may cause raised blood pressure and possibly QTc prolongation in overdose (Yekehtaz et al. 2013). Mirtazapine and trazodone have being reported to cause cardiac effects in overdose (Yekehtaz et al. 2013). The physician treating the CVD should be aware of any medications prescribed for the treatment of MDD and conjointly arrange monitoring.

5.4.4. Endocrine and autoimmune disorders

Pre-existing endocrine disorders are common in people who have MDD. Adequate treatment of the physical disorder is essential, and may improve or even resolve the depressive symptoms for example with thyroid dysfunction (Davis and Tremont 2007) and lupus erythematosus (Karol et al. 2013). Antidepressants are known to have effects on the hypothalamo-pituitary-adrenal axis, corticosteroid and immune systems, which interact with endocrine disorders (Antonioli et al. 2012). Antidepressants are commonly used for people with comorbid endocrine disorders with a good safety record, although there is a paucity of adequate safety data specific to this population.

5.4.5. Obesity

Many people seeking treatment for MDD are overweight or obese, and some antidepressants may make obesity worse or cause obesity in people who are overweight (Grundy et al. 2014). There is also evidence that obesity is associated with decreased response to antidepressants (Kloiber et al. 2007; Woo et al. 2016). Some data suggest that antidepressant-associated weight gain is more significant in females, and with longer duration of exposure (Bet et al. 2013). There are substantial differences between agents. While SSRIs have been associated with weight gain (Noordam et al. 2015), mirtazapine (Bet et al. 2013) and tricyclic antidepressants (Berken et al. 1984) are of greater concern. A study of electronic health records showed that bupropion and nortriptyline are less strongly associated with weight gain than citalopram (Blumenthal et al. 2014), although a different 6-month open-labelled study found greater weight gain for nortriptyline compared to escitalopram (Uher et al. 2009). Agomelatine has not been shown to be associated with weight gain (Demyttenaere, 2011), with data from a head-to-head comparison showing no difference in weight gain between agomelatine and an SSRI (Demyttenaere et al. 2013). Data for duloxetine also varies, with studies showing either an advantage (Wise et al. 2006) or no difference (Blumenthal et al. 2014) when compared to other antidepressants. People treated with antidepressants should be informed of the risk of weight gain and informed about options for weight control and weight reduction. Obesity is strongly associated with an increased risk of cardiovascular disease, and consequently TCAs should be avoided.

5.4.6. Bipolar disorder and risk of affective switch

People with undiagnosed bipolar disorder often present for treatment for the first time during a depressive episode. These people may experience antidepressant-associated mood elevations, either as mania or hypomania. If mood elevation or features of mixed states are observed, bipolar disorder should be

suspected (Berk et al. 2005). This is, however, a complex and controversial area, with issues in debate including the boundaries between mixed states and agitated depression, and readers are referred to recent reviews for a detailed exposition of the subject of mixed states and transition to bipolar disorder (Swann et al. 2013; Ratheesh et al. 2017).

6. Management of adverse reactions to antidepressant treatment

For most adverse reactions, the decision to alter treatment should be made on a case-by-case basis. The likelihood that the adverse reaction is associated with the antidepressant treatment and the severity of the adverse reaction should be considered. When an adverse reaction occurs, an immediate decision needs to be made to either cease treatment with the antidepressant, reduce the dose or to continue treatment without changing the treatment in response to the adverse reaction. For serious adverse reactions, such as drug-induced liver injury, immediate cessation of treatment is usually necessary. All adverse reactions should be discussed with the patient and treatment decisions made through mutual agreement.

6.1. Common adverse effects

Adverse effects that occur more commonly with antidepressants than with placebo include nausea, headaches, anxiety, sweating, sedation or fatigue, dizziness, agitation, weight gain, gastrointestinal effects and dry mouth. These effects are may be transient, although the time course of these effects has not been well studied and may differ between individuals. These adverse effects can be minimised with prudent selection of antidepressant agent and dose adjustments (Ginsberg 2009). All adverse effects may be associated with poorer treatment adherence (Shelton 2009). However many adverse events occurring with antidepressant use may be related to 'nocebo' effects (Dodd et al. 2015), where adverse events that are not due to the pharmacological properties of the treating agent emerge with treatment. Educational discussion regarding the risks and benefits of treatment and treatment strategies, as well as patient participation in decision making, can improve treatment adherence (Shelton 2009).

6.2. Sexual dysfunction

Sexual dysfunction is a common adverse effect, especially with serotonergic antidepressants, and may include altered sexual desire, erectile, ejaculatory and orgasmic dysfunction and other problems (Taylor et al. 2013). Patients should be routinely asked about sexual dysfunction as it is a common reason for non-adherence. Treatment strategies including switching to an antidepressant with a lower risk of sexual dysfunction, psychological or mechanical interventions, or drug holidays, may be considered, but are supported by limited or conflicting empirical evidence (Taylor et al. 2013). There is clinical trial evidence demonstrating the efficacy of sildenafil or tadalafil for antidepressant-induced erectile dysfunction in men, and for bupropion (150 mg b.i.d.) for antidepressant-induced sexual dysfunction in women (Taylor et al. 2013). There is also a study suggesting the utility of the 5HT3 antagonist granisetron (Berk et al. 2000), a finding reinforced by the fact that vortioxetine, a SSRI which also has 5HT3 effects seemingly has minimal sexual dysfunction (Jacobsen et al. 2016). Augmentation strategies for males and females include mirtazapine adjunctive treatment with an SSRI (Ozmenler et al. 2008) and trazodone adjunctive to treatment with an SSRI (Stryjer et al. 2009). Monitoring strategies could include the use of specific rating instruments such as the Arizona Sexual Experience Scale (ASEX) (McGahuey et al. 2000), the SFI (Fava et al. 2011), CSFQ (Clayton et al. 1997), the Psychotropic-Related Sexual Dysfunction Questionnaire (Montejo and Rico-Villademoros 2008) and the Sex Effects Scale (Kennedy et al. 2010).

6.3. Cardiotoxicity

TCAs may cause orthostatic hypotension, tachycardia, reduction in heart rate variability and slowing of intraventricular conduction, and are associated with an increased risk of myocardial infarction (Marano et al. 2011) and of sudden cardiac death in children (Goldberg and Ernst 2012). In a prospective study, TCA use in people with no known history of CVD was associated with elevated risk of CVD at an 8-year follow-up (Hamer et al. 2011). TCAs inhibit cardiovascular Na^{+}, Ca^{2+} and K^{+} channels and cause prolongation of the QT segment. This has been associated with increased risk for torsade de pointes and related arrhythmias, which may be potentially fatal. Risk factors include increasing age, comorbid cardiovascular and metabolic disease, a family history of congenital long QT syndrome, female gender, concomitant use of metabolic inhibitors and agents associated with QT interval prolongation and hypokalaemia (Vieweg and Wood 2004). Caution is required when prescribing drugs that might prolong the QT interval, especially in the context of known clinical risks. Monoamine oxidase inhibitors

frequently cause hypotension and tachycardia, and may cause hypertensive crisis (Yekehtaz et al. 2013). Newer antidepressants have better cardiac safety, but some have nevertheless been associated with arrhythmias and syncope (Pacher and Kecskemeti 2004). Citalopram was shown to dose dependently prolong the QTc interval and a caution has been declared by the US FDA for its use at doses greater than 40 mg/day (Pae et al. 2014). Management of cardiovascular adverse effects includes monitoring of heart rate and blood pressure. The involvement of co-medications should also be considered. The decision to refer a patient to specialist care may be made on a case-by-case basis (Goldberg and Ernst 2012).

6.4. Liver dysfunction

All antidepressants have been associated with drug-induced liver injury, with some drugs having more significant risks than others. Risk of drug-induced liver injury is greatest for nefazodone (which has been withdrawn from the market in some countries), phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine and agomelatine, and lowest for citalopram, escitalopram, paroxetine and fluvoxamine (Voican et al. 2014; Friedrich et al. 2016). Drug-induced liver injury is most likely to occur in the first 6 months from initiating antidepressant therapy, although the latency can vary with agent (Lucena et al. 2003). Where raised serum aminotransferase levels or signs or symptoms of liver injury are detected, antidepressant use should be considered as a probable cause. Drug-induced liver injury may be hepatocellular, cholestatic, or mixed hepatocellular-cholestatic, and can be mild, moderate or severe (Fontana et al. 2010). Patients who experience acute liver injury may present with fatigue, nausea, abdominal pain, fever, dark urine, jaundice or pruritis (Fontana et al. 2010). Biochemical LFTs should be used to monitor liver health. Specialist care may be required. Other causes should be sought, such as covert alcohol use. Antidepressant rechallenge may be considered after the serum transaminase levels have returned to the normal range, preferably with a different antidepressant.

6.5. Hyponatraemia

Hyponatraemia, defined as a serum sodium concentration below 135 mmol/l (Nagler et al. 2014), is common in elderly people and may worsen with antidepressant treatment. Treatment strategies vary depending on severity and acuity. All strategies are aimed at restoring normal levels of sodium (Nagler et al. 2014). Fluid restriction to 1 l/day is a recommended treatment for mild antidepressant-associated hyponatraemia (Goldberg and Ernst 2012). Interruption of antidepressant treatment during hyponatraemia treatment has been suggested (Martinez-Cortes et al. 2013). Other co-medications, especially diuretics, may also be considered. Alternatives to the specific antidepressant treatment might be considered.

6.6. Serotonin syndrome

Serotonin syndrome is the possible result of excessive serotonin receptor antagonism and not necessarily an idiopathic drug reaction (Boyer and Shannon 2005). Serotonin syndrome is diagnosed by clinical symptoms suggestive of CNS hyper-excitability co-occurring with drug-induced increased serotonin. Symptoms vary between cases and may be mild to life threatening. Common symptoms include; confusion, consciousness impairment, agitation, tremor, hyperreflexia, myoclonus, tachycardia, hypertension and fever. In more severe cases rhabdomyolysis, clonus, rigidity/hypertonicity, elevated temperature, fever or hyperthermia may be evident (Werneke et al. 2016). Treatment of serotonin syndrome requires stopping the serotonergic agent in all cases. Intensity of treatment depends on the severity of illness however, treating clinicians should be aware that some cases may deteriorate without aggressive management. Cardiorespiratory and thermal abnormalities must be aggressively corrected (Boyer and Shannon 2005). Cyproheptadine is a recommended therapy, although other agents have been used (Boyer and Shannon 2005).

6.7. Other serious adverse effects

Reports exist of rare, but potentially life-threatening antidepressant adverse effects. At least two cases of agranulocytosis with mirtazapine have been reported (Goldberg and Ernst 2012). Where blood dyscrasias occur, the causative agent should be ceased. Antidepressants are associated with increased risk of seizures, especially for TCAs and also for bupropion (in doses above 450 mg/day), where risk can be reduced through dose reduction (Mago et al. 2008). Antidepressant-induced extrapyramidal symptoms and/or akathisia are rare but can be associated with significant morbidity and decreased quality of life (Lane 1998; Madhusoodanan et al. 2010). Gastrointestinal (GI) bleeding has been reported for patients using serotonin reuptake inhibitors which impair platelet function (Bismuth-Evenzal et al. 2012), most commonly with concomitant use of aspirin,

nonsteroidal anti-inflammatory drugs (NSAIDs), or other medications that may affect haemostasis (Mago et al. 2008; Anglin et al. 2015) and antidepressant and NSAID combinations have been associated with an increased risk of intracranial haemorrhage (Shin et al. 2015). Protective strategies against GI bleeding include co-administration of a proton pump inhibitor or an H_2 histamine blocker (Goldberg and Ernst 2012).

7. Management of deliberate or accidental antidepressant overdose

Antidepressants, especially older medications such as TCAs, can be fatal in overdose (Henry et al. 1995; Frey et al. 2000). During TCA overdose, seizures and arrhythmias may occur. Rapid deterioration is common and death or serious complications typically occur within 24 h (Thanacoody and Thomas 2005). Newer antidepressants have a better safety profile in overdose. The fatal toxicity index (FTI), a measure of the number of deaths due to overdose per million prescriptions is highest for TCAs, ranging from desipramine (FTI 201) to amitriptyline (FTI 38), and the MAOI tranylcypromine (FTI 44) (Buckley and Faunce 2003), but lower for venlafaxine (FTI 4.4) and mirtazapine (FTI 2.6), and lowest for SSRIs ranging from fluvoxamine (FTI 1.5) to sertraline (FTI 0.38) and fluoxetine (FTI 0.33) (Koski et al. 2005).

Emergency management of overdoses will be influenced by the antidepressant involved, the drug's metabolism and half-life, and patient specific factors such as whether other drugs or alcohol were included in the overdose. In general, a strategy of supportive medical care can be employed. First line treatments include strategies for reducing absorption, gastric lavage and administration of activated charcoal (Kerr et al. 2001). Alkalinisation by sodium bicarbonate administration or by hyperventilation is beneficial for TCA overdose (Kerr et al. 2001). A case report suggests that sodium bicarbonate may be useful for venlafaxine overdose (Buckley and Faunce 2003), but there are no reports suggesting benefit for other newer antidepressants. Seizure associated with antidepressant overdose can be managed with airway protection and benzodiazepines (Buckley and Faunce 2003).

8. Conclusions

Antidepressant treatments may be associated with a complex array of risks, requiring careful assessment and monitoring. Treatment with antidepressants should therefore balance risks against benefits. Adverse events can be minimised by following safety monitoring recommendations, which can also be helpful for detecting and assessing adverse effects when they occur. Management strategies for adverse events can be used to optimise care. Safe prescribing of antidepressant requires recognition of individual risk factors and a thoughtful assessment of how these risk factors interplay with different antidepressant choices, co-medications, and other patient factors.

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