67 - Psychological symptoms of the menopause

Psychological symptoms of the menopause

858 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 10 Psychological symptoms of the menopause Depression and anxiety The impact of the menopause on mental well-being is significant. Suicidal ideation is present in around 6% of women experiencing menopause-related psychological symptoms. There is a 2–5-fold increase in the risk of depression during the perimenopause.4 Hormone replacement therapy (HRT) is first-line treatment for menopausal insomnia, anxiety and depression.1 Psychosis The decline in production of protective oestrogens is thought to be the reason that women show an increased risk of psychosis later in life (particularly at menopause) that is not observed in men, with one study suggesting that first hospital admission rates for psychosis are twice as high in women (21%) than in men (10%) after the age of 40. Pharmacodynamics Oestrogen is thought to have complex effects on dopamine transmission and receptor sensitivity, as well as antipsychotic binding. Human positron emission tomography (PET) studies have revealed that women have more D2 receptors in the brain compared with men. As oestrogen is thought to enhance antipsychotic binding affinity to these receptors, declining oestrogen levels in menopause serve to reduce antipsychotic activity.5–7 Consequently, many women require higher doses of antipsychotic medication after menopause to maintain previous effect.8 Pharmacokinetics Gender variations in the pharmacokinetics of psychotropic drugs are often not considered but may play an important role in drug efficacy and adverse effects. Factors such as gastrointestinal transit time, drug distribution of lipophilic drugs (e.g. antipsychotics) and drug elimination can vary with age and with hormonal changes seen during and after menopause.9 Oestrogen and progesterone can decrease levels of glycoproteins responsible for binding to antipsychotic drugs. Declining levels of these hormones may therefore result in less free drug entering the brain.9 Oestrogens are also thought to influence the activity and expression of some of the enzymes responsible for the hepatic metabolism of antipsychotics, i.e. oestrogens can induce and inhibit CYP isoenzymes (Table 10.21).9 Alternative treatments and drug interactions Polypharmacy in menopausal women is common, with many women using alternative treatments (such as herbal remedies) to address menopausal symptoms. It is important that drug interactions are ruled out when prescribing antipsychotic medication.10 The use of several medications, for example for sleep, pain and depression, may also affect protein binding of concurrent

antipsychotics leading to changes in the ability for certain drugs to enter the brain.5

Drug treatment of psychiatric symptoms in the context of other conditions CHAPTER 10 Long--acting injections (LAIs) Switching to an antipsychotic depot may improve levels of drugs that are mainly hepatically metabolised by CYP enzymes, as first-pass metabolism is avoided.6 The use of antipsychotic depot injections should be considered if oral medications appear to lose efficacy in menopause.10 Longer dosage intervals for LAIs may be beneficial in menopause as older women tend to eliminate drugs more slowly than their male counterparts.12 Risk of adverse effects Increasing age coupled with oestrogen loss in menopause can make women more vulnerable to antipsychotic-related adverse effects. Older women are more vulnerable to QTc prolongation and motor symptoms (parkinsonism, akathisia and tardive dyskinesia) and therefore it is best to avoid antipsychotic drugs that may worsen these adverse effects.8 Increased adiposity in menopause may be associated with a heightened risk for Table 10.21 Summary of antipsychotic/oestrogen interactions.5,8,11 Isoenzyme Substrates Effect of oestrogen on enzyme activity Recommendations CYP1A2 Clozapine, olanzapine Inhibits Oestrogen is thought to inhibit/reduce CYP1A2 activity and thus doses of antipsychotics that are mainly metabolised by this isoenzyme may need to be increased at menopause. Extra care should be given to antipsychotic dosing in menopausal women who smoke. CYP3A4 Aripiprazole, quetiapine, lurasidone Induces Women generally have a higher expression of CYP3A4 enzyme than men, and menopause may cause reduced expression of this enzyme. High levels of oestrogen in pregnancy are thought to increase the metabolism via CYP3A4, further suggesting that oestrogen (and progesterone) play a role in rate of hepatic drug metabolism. Lower doses of CYP3A4-metabolised antipsychotics may be required in menopause, particularly if onset of menopause causes an increase in adverse effects. CYP2D6 Aripiprazole, haloperidol, risperidone, zuclopenthixol Possibly induces CYP2D6 activity is generally higher in women than men. The clinical relevance of increased activity may be small, particularly as there may be genetic variations in the CYP2D6 gene. Some evidence suggests that doses of aripiprazole may require lowering at menopause (this may also be because it is metabolised by CYP3A4). CYP2C19 Clozapine (minor route) Possibly inhibits Females reportedly have a 40% lower enzyme activity than men. This difference is thought to be most pronounced from 18 to 40 years (generally prior to onset of menopause). As stated previously, clozapine doses may need to be higher in menopausal women, however this needs to be balanced against risk of adverse effects. More regular therapeutic drug monitoring may be required.

860 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 10 adverse effects such as insulin resistance, diabetes, sleep apnoea, cardiovascular disease and hypertriglyceridaemia.13 Prolactin levels Persistently high prolactin levels may cause hypo-oestrogenic states and subsequently induce iatrogenic menopause.12 This may worsen psychotic symptoms and cognition5 as well as further increase the risk of osteoporosis in an already vulnerable group.8,13 There is some evidence to suggest that high prolactin levels can also increase the risk of breast cancer.13 Genitourinary problems and sexual dysfunction (including diminished libido) are issues that can be troublesome due to menopause and can be further worsened by hyperprolactinaemia.12 It is important to note that hormones other than prolactin and oestrogen (e.g. progesterone) may play a potentially key role when considering antipsychotic use in menopause, although further research is required in this area.5 Oestrogen augmentation for psychosis Treatment with adjunct oestrogenic medications may be beneficial in helping to relieve menopausal symptoms as well as improving psychotic symptoms and increasing the efficacy of antipsychotic drugs.8 Recent meta-analyses have shown that selective oestrogen

receptor modulators (SERMs) such as raloxifene (60–120mg/day) are a safe and effective adjunct for treating schizophrenia in menopausal women.14 Raloxifene may be more suitable for long-term use than HRT as it has oestrogenic effects on the brain and bone tissue but anti-oestrogenic effects on other tissues such as the breast and uterus (therefore reducing the risk of breast and uterine cancer).8,15 Both HRT and SERMs may increase the risk of venous thromboembolism (VTE)16 and so potential risks and benefits of using these drugs as oestrogen-augmenting agents should be balanced individually, for example oestrogen replacement therapy may not be appropriate for those with a history of thromboembolic conditions.8 The preferred options for treating menopausal women with antipsychotic medications are summarised in Box 10.7. Box 10.7 Summary of preferred antipsychotic options for menopausal women8,12 First option(s): aripiprazole, lurasidone Second option(s): olanzapine, quetiapine, clozapine Avoid where possible: amisulpride, risperidone, paliperidone and FGAs Monitor: weight, bone mineral density, blood pressure, blood glucose, cholesterol and prolactin levels (especially if using prolactin-raising antipsychotics); therapeutic drug monitoring – due to hormonal fluctuations17 ■ ■Consider augmentation with raloxifene or HRT at an early stage, i.e. at the beginning of menopause/perimenopausal stage, where appropriate15,18 ■ ■If the efficacy of previously effective antipsychotic doses wanes at menopause, review the drug dose ■ ■Be mindful of the risk of dose-related adverse effects such as weight gain and cardiovascular and cerebrovascular events6 ■ ■Switching to prolactin-sparing medications can benefit both mental and physical health13 ■ ■Consider adding anti-diabetic drugs (where appropriate) such as metformin which may help to prevent excess weight gain19 ■ ■Consider using LAIs as an option if oral medication becomes ineffective6 HRT, hormone replacement therapy; LAIs, long-acting injections.

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