18 - Psychotropics and the risk of seizures in peo

Psychotropics and the risk of seizures in people with epilepsy

814 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 10 Pharmacodynamic interactions14 Adverse effects with antiseizure medications that may overlap with psychotropic adverse effects include: ■ ■Weight gain: caused by some antiseizure medications (e.g. carbamazepine, gabapentin, pregabalin, valproate). ■ ■Sexual adverse effects: with phenobarbital and primidone but possible with all enzyme-inducing antiseizure medications. ■ ■Hyponatraemia: with carbamazepine and oxcarbazepine (note, if severe, can provoke seizures). ■ ■Osteoporosis and osteopenia: reported with long-term use of enzyme-inducing antiseizure medications. ■ ■Blood dyscrasias: reported with valproate, carbamazepine11 and especially with felbamate. Psychotropics and the risk of seizures in people with epilepsy In the general population, the annual incidence of unprovoked seizures is about 50 per 100,000 persons.24,25 It is notable that the incidence of unprovoked seizures in the placebo arms of randomised controlled trials of antidepressants and antipsychotics is approximately 15-fold higher, suggesting that both depression and psychosis are risk factors for seizures.26 A bidirectional relationship between epilepsy and several psychiatric illnesses has been demonstrated, whereby not only do PWE have a higher risk of developing a psychiatric illness, but people with psychiatric illness have a higher risk of developing epilepsy.5,6 This bidirectional relationship exists for depression, anxiety, psychosis and suicidality.5–7 Thus, the occurrence of seizures may, in some cases, be the expression of the natural progression of a psychiatric illness and be unrelated to the use of psychotropics. Reports of seizures associated with psychotropics must factor in this bidirectional relationship between psychiatric illness and epilepsy. For example, although observational studies have reported an association between antidepressant treatment and seizures,27 a similar association is also found with non-drug treatments for depression (counselling, for example).28 These findings are consistent with depression itself being the main risk factor for seizures. In fact, one analysis of controlled studies with psychotropics showed that the incidence of seizures was substantially lower

among patients receiving most antidepressants (e.g. SSRIs) in comparison with those randomised to placebo.26 Nonetheless, definitive data are lacking in PWE29,30 and certain psychotropics have a dose-related risk of seizures within usual dose ranges. Most can cause seizures in overdose. Note also that almost all antidepressants and antipsychotics have been associated with hyponatraemia (see sections on hyponatraemia in Chapters 1 and 3) and seizures may occur if this is severe.18,31 General guidance on the safety of psychotropics in PWE is summarised in Table 10.5. Electroconvulsive therapy (ECT) has anticonvulsive properties and is worth considering in the treatment of depression in patients with unstable epilepsy.9,18,23 ECT does not appear to cause or worsen epilepsy.18,32

Drug treatment of psychiatric symptoms in the context of other conditions CHAPTER 10 Table 10.5 Psychotropics in epilepsy. Safety in epilepsy Drug Comments Antidepressants Low risk – good choices33 SSRIs Recommended in PWE.15,19 SSRIs may be anticonvulsant at therapeutic doses14 but proconvulsant in overdose.34 SSRIs with the lowest risk of interactions with antiseizure medications are generally preferred (citalopram/escitalopram, followed by sertraline).15,19,35,36 Escitalopram is preferred over citalopram in PWE (lower risk of seizures in overdose).37 Others have low risk of seizures (e.g. fluoxetine37) but drug interactions with antiseizure medications should be considered.15,19 Fluoxetine may be less likely to provoke seizures in older people than escitalopram or citalopram.38 Some evidence that sertraline is safe and effective in PWE.39 Mirtazapine Recommended in PWE.19,40 Not known to be proconvulsive.26 Duloxetine Recommended for PWE.12,19 Risk of seizures is probably negligible.37,38 Probably low risk – use with caution (limited evidence) Agomelatine Not known to be proconvulsive.41 Anticonvulsant in animal models.37 MAOIs Not known to be proconvulsive at therapeutic doses.37 Low risk of seizures in overdose.18 Moclobemide Not known to be proconvulsive.37 Anticonvulsant in animal models.37 Reboxetine Small open-label study suggests no problems in PWE.42 Vortioxetine Not known to be proconvulsive.37,43 One report of successful use of vortioxetine in three PWE.44 Moderate risk – care required Lithium Low risk of seizures.37 Anticonvulsant in animal models.37 However, limited data showing both increases and decreases in seizures frequency in PWE.37 At standard plasma levels lithium is probably not proconvulsive.45 For bipolar, consider anticonvulsant mood stabilisers.46 Trazodone Limited data suggest some risk of seizures.37,47 Venlafaxine Effective in PWE12 and has been recommended19 but mixed evidence on seizure risk.37 Vilazodone Limited data. Seizure exacerbation in a patient with epilepsy has been reported.37 Higher risk – avoid (proconvulsive at therapeutic doses14) Amoxapine Several reports of seizures at therapeutic doses47 Bupropion Dose-related risk of seizures (particularly with immediate-release formulations).37 Risk is less with slow-release formulations at doses under 300mg/day.37 At least one study found no increased risk with bupropion.48 Maprotiline Several reports of seizures at therapeutic doses.47 TCAs Most TCAs are epileptogenic at higher doses (particularly clomipramine and amitriptyline11,26,47). Doxepin possibly lower risk (one small study in PWE).37 SNRIs are preferred over TCAs in PWE18 (Continued)

816 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 10 Table 10.5 (Continued) Safety in epilepsy Drug Comments Antipsychotics Low risk – good choices Amisulpride/sulpiride Considered to be safe in PWE.49 Renally excreted, so low risk of pharmacokinetic interactions with antiseizure medications. Seizures uncommon in overdose.50 Aripiprazole Rarely lowers seizure threshold.5 Incidence of seizures similar to placebo in RCTs.26 Ziprasidone High-potency FGAs e.g. fluphenazine, haloperidol, trifluoperazine, flupentixol. Low risk of lowering the seizure threshold.5 Risperidone Unlikely to lower the seizure threshold.5 Incidence of seizures similar to placebo in

RCTs.26 Has been recommended for PWE.35,51 Evidence of safety in a case series of adolescents with epilepsy.52 Probably low risk – use with caution (limited evidence) Asenapine Seizure rate similar to placebo in RCTs.53 Data and clinical experience of use in PWE is extremely limited. Brexpiprazole Cariprazine Lurasidone Moderate risk – care required Olanzapine Olanzapine and quetiapine both associated with seizures in RCTs.26 Overall risk of reducing the seizure threshold is considered to be low5 and olanzapine has been recommended by some for PWE.35 Data relating to olanzapine are difficult to interpret. EEG changes are seen in some but not all studies54 and it has been reported to be both anticonvulsant55 and proconvulsant.56 Quetiapine has a high risk of drug interaction in PWE.51 Quetiapine Higher risk – care required Clozapine Most proconvulsive antipsychotic.35 However, has been used successfully in PWE stable on antiseizure medications without worsening seizures57 and even in treatment-resistant epilepsy.58 Note, should not be used with carbamazepine (risk of blood dyscrasias and reduced clozapine levels). Lamotrigine is the antiseizure medication of choice. Higher risk – avoid Low-potency FGAs (e.g. chlorpromazine) Best avoided in PWE.34 Doses of chlorpromazine above 1g/day have a 9% incidence of seizures. Loxapine Highest rate of seizures among the FGAs.59 Depot antipsychotics None of the depot preparations currently available is thought to be epileptogenic, however the kinetics of depots are complex (seizures may be delayed). If seizures do occur, the offending drug may not be easily withdrawn. Depots should be used with extreme care. Zotepine Has established dose-related proconvulsive effect50 Drugs for ADHD Low risk Methylphenidate Three RCTs support safety and efficacy in children with epilepsy at therapeutic doses (0.3–1mg/kg/day).11 Two single-dose RCTs and one open-label extension study demonstrated no effect on seizures in adults.60,61 A large case–control study found an increased rate of seizures after the start of methylphenidate but not in the longer term.62 This is difficult to interpret but suggests caution would be appropriate. May be a higher risk of seizures at higher doses.63

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