59 - Psychostimulants in depression

Psychostimulants in depression

388 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Psychostimulants in depression Psychostimulants reduce fatigue, promote wakefulness and can be mood elevating. Amfetamines have been used as treatments for depression since the 1930s1 and more recently modafinil has been evaluated as an adjunct to standard antidepressants. Amfetamines are now rarely used in depression because of their propensity for the development of tolerance and dependence. Prolonged use of high doses is associated with psychosis.2 Methylphenidate is now more widely used than amfetamines but may have similar shortcomings. Modafinil seems not to induce tolerance, dependence or psychosis but lacks the marked euphoric effects of amfetamines. Armodafinil, the longer-acting isomer of modafinil, is available in some countries. Psychostimulants differ importantly from standard antidepressants in that their mood-elevating effects are usually seen within a few hours, but their antidepressant action may be short lived. Amfetamines and methylphenidate may thus be useful where a prompt effect is required and where dependence would not be problematic (e.g. in depression associated with terminal illness), although ketamine might also be considered in these cases. Their use might also be justified in severe, prolonged depression unresponsive to standard treatments (e.g. in those considered for psychosurgery). Modafinil might justifiably be used as an adjunct to antidepressants in a wider range of patients and as a specific treatment for hypersomnia and fatigue.3 Table 3.10 outlines support (or the absence of it) for the use of psychostimulants in various clinical situations. Generally speaking, data relating to stimulants in depression are rather poor and inconclusive.4,5 A network meta-analysis6 concluded that although psychostimulants (particularly methylphenidate) seem to be well tolerated and have some efficacy in depression, the strength of evidence is very low and insufficiently consistent to provide any definitive hierarchy of treatments. Careful consideration should be given to any use of any psychostimulants in depression, since their short- and long-term safety have not been clearly established. Inclusion of individual drugs in Table 3.10 should not in itself be considered a recommendation for their use. (Continued) Table 3.10 Stimulants in depression. Clinical use Regimens evaluated Comments Recommendations Monotherapy in uncomplicated depression Modafinil 100–200mg/day7,8 Case reports only – efficacy unproven Standard antidepressants preferred. Avoid psychostimulants as monotherapy in uncomplicated

depression.9 Meta-analysis found adjunctive therapy but not monotherapy to be associated with clinically significant improvements.5 Methylphenidate 20–40mg/day10,11 Minimal efficacy Dexamfetamine 20mg/day10 Minimal efficacy

Depression and anxiety disorders CHAPTER 3 Table 3.10 (Continued) (Continued) Clinical use Regimens evaluated Comments Recommendations Adjunctive therapy to accelerate or improve response SSRI + methylphenidate 10–20mg/day12,13 No clear effect on time to response Psychostimulants in general not recommended, but modafinil may be useful SSRI + modafinil 400mg/day6 Improved response over SSRI alone Tricyclic + methylphenidate 5–15mg/day14 Single open-label trial suggests faster response SSRI or SNRI + lisdexamfetamine 20–70mg/day15 No superiority over placebo Adjunctive treatment of depression with fatigue and hypersomnia SSRI + modafinil 200mg/day6,16 Beneficial effect only on hypersomnia. Modafinil may induce suicidal ideation. Possible effect on fatigue, but weak evidence. An option where fatigue is prominent and otherwise unresponsive. SSRI + methylphenidate 10–40mg/day17 Clear effect on fatigue in hospice patients Adjunctive therapy in treatmentresistant depression SSRI + modafinil 100–400mg/ day5,6,18–21 Effect mainly on fatigue and daytime sleepiness. Meta-analysis of 10 trials suggested clinically significant improvement in depressive symptoms.5 Data limited. Modafinil may be useful for fatigue22 and cognition.23 MAOI + dexamfetamine 7.5–40mg/day24 or lisdexamfetamine 50mg/ day25 Support from single case series and one case report Stimulants an option in refractory illness but other options better supported. One naturalistic study suggests methylphenidate may reduce self-harm or suicide attempts.26 Methylphenidate or dexamfetamine +/– antidepressant27 Large case series (n = 50) suggests benefit in the majority Lisdexamfetamine 20–70mg/ day + antidepressant5,15,28 Two meta-analyses found a small, non-significant effect on depressive symptoms compared with placebo Adjunctive treatment in bipolar depression29,30 Mood stabiliser and/or antidepressants + modafinil 100–200mg/day31 Significantly superior to placebo Possible treatment option where other standard treatments fail. Meta-analysis of trials referenced here found stimulants well tolerated and an overall benefit vs placebo.32 No evidence of treatment- emergent mania.29,32–34 Mood stabiliser + armodafinil 150–200mg/day33 (one case report of 1000mg/day35) Superior to placebo on some measures Mood stabiliser + methylphenidate 10–40mg/ day36 Mixed results, mainly positive Mood stabiliser and/or antipsychotic + lisdexamfetamine 20–70mg/day37 Greater rates of improvement compared with placebo on patient-rated measures

390 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Table 3.10 (Continued) Clinical use Regimens evaluated Comments Recommendations Monotherapy or add-on treatment in late--stage terminal cancer Methylphenidate 5–30mg/ day38–42 Case series and open prospective studies Useful treatment options in those expected to live only for a few weeks Dexamfetamine 2.5–20mg/ day43,44 Beneficial effects seen on mood, fatigue and pain Methylphenidate 20mg/day + mirtazapine 30mg/day45 RCT shows benefit for combination from third day of treatment Methylphenidate 20mg/day + SSRI46 RCT failed to show benefit for combination Modafinil 200mg/day47 Benefit to depression scores only in those also experiencing severe cancer-related fatigue Monotherapy or add-on treatment for depression in the elderly Methylphenidate 1.25–20mg/ day48–50,51 Use supported by four placebo-controlled studies. Rapid effect observed on mood and activity. Recommended only where patients fail to tolerate standard antidepressants or where contraindications apply Methylphenidate 5–40mg + citalopram 20–60mg/day52 Four studies from the same group, two RCTs. Faster rate of response with combination compared with monotherapy with either drug. Significant increase in heart rate seen in one trial Monotherapy in

post-stroke depression Methylphenidate 5–40mg/ day53–56 Variable support but including two placebo- controlled trials.53,56 Effect on mood evident after a few days. Standard antidepressants preferred. Further investigation required: stimulants may improve cognition and motor function. Modafinil 100mg/day57 Single case report Monotherapy in depression secondary to medical illness Methylphenidate 5–20mg/ day58 Limited data Psychostimulants not appropriate therapy. Standard antidepressant preferred. Dexamfetamine 2.5–30mg/ day59,60 Monotherapy in depression and fatigue associated with HIV Dexamfetamine 2.5–40mg/ day61,62 Supported by one good, controlled study.62 Beneficial effect on mood and fatigue. Possible treatment option where fatigue is not responsive to standard antidepressants Monotherapy in depression in traumatic brain injury Methylphenidate 5–20mg/ day63 Improves depressive symptoms, daytime sleepiness and cognitive function Appears to outperform antidepressants for this indication, but data are limited to two studies

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