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Neurobiology of withdrawal

120 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Neurobiology of withdrawal Withdrawal-associated relapse has been attributed to neural adaptations to long-term antipsychotic treatment (dopaminergic hypersensitivity, among other effects) that persist after antipsychotic cessation.24 Indeed, molecular imaging studies in schizophrenia have found increased D2/D3 receptor availability in those patients who had been exposed to antipsychotic medication but not in antipsychotic-naïve patients.25 This hypersensitivity to dopamine may render patients more susceptible to psychotic relapse when D2 blockade is diminished by antipsychotic dose reduction.11,24 There are converging lines of evidence that suggest that the neuroadaptive effects of antipsychotics can persist for months or years after stopping. Dopaminergic hypersensitivity in animals persists for the equivalent of a human year after treatment is stopped.26,27 TD – widely attributed to dopaminergic hypersensitivity – can persist for years after antipsychotic medication has been ceased.28 There is also evidence that patients who have discontinued antipsychotics have increased rates of relapse for 3 years compared with people maintained on their antipsychotics, after which relapse rates converge,1 perhaps suggesting that adaptations may have resolved by this point. Persisting dopaminergic hypersensitivity may lower the threshold for precipitating relapse from other triggers for as long as they persist (which may be months or years).20 It follows that the risk of relapse on cessation of antipsychotics might be minimised by more gradual dose tapering because these neuroadaptations would then have time to resolve during the tapering process and the rate of decline of receptor antagonism is more modest.20 Studies in which antipsychotics are tapered over months or years show reduced rates of relapse compared with relatively faster tapers,23,29,30 with one study finding that reducing dose over a year reduced the hazard rate of relapse by 3.5-fold compared with reducing over days.29 Cholinergic withdrawal symptoms Agitation, insomnia, anxiety or depression Dizziness, light-headedness, tachycardia Nausea, vomiting, salivation Diarrhoea, abdominal cramp Tremor, parkinsonism, restlessness Myalgia, rigidity, paraesthesia Agitation, fear, hallucinations Confusion or disorientation Hypothermia, sweating Histaminergic withdrawal symptoms Irritability, insomnia, agitation Depressed affect Loss of appetite or nausea Tremulousness, incoordination Lethargy or amnesia Dopaminergic withdrawal symptoms – nigrostriatal Withdrawal dyskinesia Parkinsonism Neuroleptic malignant syndrome Akathisia Antipsychotic withdrawal syndrome Dopaminergic withdrawal symptoms – mesolimbic or striatal Auditory hallucinations Persecutory delusions Other psychotic symptoms Serotonin withdrawal symptoms Flu-like symptoms, sweating or chills, dizziness, lightheadedness or tachycardia Paraesthesia, electric shock sensations Anxiety,

agitation, low mood Insomnia, nightmares Nausea, vomiting, diarrhoea Confusion, decreased concentration Adrenergic withdrawal symptoms Headache, anxiety or agitation Hypertension, tachycardia, angina, palpitations Risk of myocardial infarction Presyncope, tremulousness Sweating Figure 1.2 Antipsychotic withdrawal symptoms. Source: adapted from Chouinard et al. (2017).12

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