38 - Pharmacological treatment of negative symptom

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34 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Negative symptoms Negative symptoms in schizophrenia represent the absence or diminution of normal behaviours and functions and constitute an important dimension of psychopathology. A subdomain of ‘expressive deficits’ manifests as a decrease in verbal output and verbal expressiveness, and flattened or blunted affect, which is assessed by diminished facial emotional expression, poor eye contact, decreased spontaneous movement and lack of spontaneity. A second ‘avolition/amotivation’ subdomain is characterised by a subjective reduction in interests, desires and goals, and a behavioural reduction in purposeful acts, including a lack of self-initiated social interactions.1,2 While there is some consensus around this two-dimensional model, five-factor models of negative symptoms have also been propounded.3,4 Persistent negative symptoms are held to account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.5–8 The aetiology of negative symptoms is complex, and it is important to determine the most likely cause in any individual case before embarking on a treatment regimen. An important clinical distinction is between primary negative symptoms, which constitute an enduring deficit state, predict a poor prognosis and are stable over time, and secondary negative symptoms, which are consequent upon positive psychotic symptoms, depression or demoralisation, or adverse medication effects, such as dysphoria and bradykinesia as part of drug-induced parkinsonism.7,9 Other sources of secondary negative symptoms may include chronic substance or alcohol use, high-dose antipsychotic medication, social deprivation, lack of stimulation and hospitalisation.10 Secondary negative symptoms may be best tackled by treating the relevant underlying cause. In people with established schizophrenia, prominent, clinically relevant negative symptoms are seen in around 60%, with up to 20% judged to have persistent, primary negative symptoms.11–13 The literature pertaining to the pharmacological treatment of negative symptoms partly comprises sub-analyses of acute efficacy studies, correlational analyses and path analyses.14 There is often no

reliable distinction between primary and secondary negative symptoms or between the two subdomains of expressive deficits and avolition/ amotivation, and relatively few studies specifically recruit patients with persistent or predominant negative symptoms. While the evidence suggests short- and medium-term efficacy for a few interventions, there is no widely accepted evidence for an effective treatment for persistent primary negative symptoms. Pharmacological treatment of negative symptoms ■ ■In first-episode psychosis, the presence of negative symptoms is related to poor outcome in terms of recovery and level of social functioning.6,11 There is evidence to suggest that the earlier a psychotic illness is effectively treated, the less likely is the development of negative symptoms over time.15–17 However, when interpreting such data, it should be borne in mind that an early clinical picture characterised by negative symptoms, being a less socially disruptive and more subtle signal of psychotic illness than positive symptoms, may contribute to delay in presentation to clinical services and thus be associated with a longer duration of untreated psychosis. In other words, patients with an inherently poorer prognosis in terms of persistent negative symptoms may be diagnosed and treated later.

Schizophrenia and related psychoses CHAPTER 1 ■ ■While antipsychotic medication has been shown to improve negative symptoms, this benefit has mainly been shown in secondary negative symptoms in acute psychotic episodes.18 Against expectations, there is no consistent evidence for the superiority of SGAs over FGAs in the treatment of negative symptoms.19–23 Similarly, early analyses found no consistent evidence for the superiority of any individual SGA.24 A 2015 meta-analysis of 38 RCTs found a statistically significant reduction in negative symptoms with SGAs, but the effect size did not reach a threshold for ‘minimally detectable clinical improvement over time’.25 ■ ■There are some relatively robust data suggesting superior efficacy for negative symptoms with certain antipsychotics, such as cariprazine,26–28 aripiprazole and amisulpride, and single trials suggesting that olanzapine and quetiapine may be more effective than risperidone.26,29–37 A 2023 review included amisulpride and cariprazine among the medications considered to have the most promise as treatments for primary negative symptoms.38 ■ ■While clozapine remains the only medication with convincing superiority for TRS, whether or not it has superior efficacy for negative symptoms in such cases, at least in the short term, remains uncertain.39–41 One potential confound in studies of clozapine for negative symptoms is that the medication has a low liability for parkinsonian adverse effects, including bradykinesia. These are symptoms which have a phenomenological overlap with negative symptoms, particularly the subdomain of expressive deficits. There is some evidence to suggest that for patients being treated with clozapine who have residual negative symptoms, the addition of cariprazine may help.42,43 ■ ■With respect to the effect of decreasing glutamate transmission on negative symptoms, three meta-analyses have suggested a beneficial response with add-on memantine44–46 but there have been inconsistent meta-analysis findings for lamotrigine augmentation of clozapine.47,48 Adding minocycline, an antibiotic and inflammatory drug, initially showed promise46,49,50 but a relatively large RCT of adjunctive minocycline found it was not efficacious in treating negative symptoms.51 Further, the BeneMin study,49 which was designed to determine whether adjunctive minocycline, administered early in the course of schizophrenia, protected against the development of negative symptoms over a year, also failed to find any evidence of clinical benefit. The glutamate antagonist topiramate may have some efficacy for symptom reduction in schizophrenia spectrum disorders, including negative symptoms.52 ■ ■A 2006 Cochrane review concluded that antidepressant augmentation of an antipsychotic for negative symptoms may be an effective strategy for reducing affective flattening, alogia and avolition.53 RCTs and meta-analyses addressing antidepressant augmentation of antipsychotic medication have yielded somewhat inconsistent evidence of modest

efficacy.54–59 One meta-analysis of placebo-controlled studies in people with established schizophrenia found that adjunctive antidepressant treatment was associated with a limited reduction in negative symptoms, and only when added to treatment with FGAs.58 Another review of meta-analyses concluded that the evidence suggested a beneficial effect for some SSRIs, such as fluvoxamine, citalopram, and the α2 receptor antagonists mirtazapine and mianserin.18 Reboxetine (a noradrenaline reuptake inhibitor) may also have some activity.60 ■ ■A host of other augmentation agents have been tested.46,61,62 For example, meta- analyses provide some support for adjunctive treatment with Ginkgo biloba63 and a COX-2 (cyclooxygenase-2) inhibitor (albeit with a small effect size),64 while small

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