05 - Relative efficacy

Relative efficacy

Schizophrenia and related psychoses CHAPTER 1 Antipsychotics are effective in both the acute and maintenance treatment of schizophrenia and other psychotic disorders. They differ in their pharmacology, pharmacokinetics, overall efficacy/effectiveness and tolerability, and, perhaps more importantly, response and tolerability differ between patients. This variability of individual response means that there is no clear first-line antipsychotic medication that is preferable for all. Relative efficacy After the publication of the independent CATIE4 and CUtLASS5 studies, the World Psychiatric Association reviewed the evidence relating to the relative efficacy of 51 FGAs and 11 SGAs and concluded that, if differences in EPS could be minimised (by careful dosing) and anticholinergic use avoided, there was no convincing evidence to support any advantage for SGAs over FGAs.6 As a class, SGAs may have a lower propensity for EPS and tardive dyskinesia (TD),7 but this was somewhat offset by a higher propensity to cause metabolic adverse effects. A meta--analysis of antipsychotic medications for first-episode psychosis8 found few differences between FGAs and SGAs as groups of drugs but minor advantages for olanzapine and amisulpride individually. A later network meta-analysis of first-episode studies found small efficacy advantages for olanzapine and amisulpride and overall poor performance for haloperidol.9 When individual non-clozapine SGAs are compared, summary data suggest that olanzapine is marginally more effective than aripiprazole, risperidone, quetiapine and ziprasidone, and that risperidone has a minor advantage over quetiapine and ziprasidone.10 FGA-controlled trials also suggest an advantage for olanzapine, risperidone and amisulpride over older drugs.11,12 A network meta--analysis13 broadly confirmed these findings, ranking amisulpride second behind clozapine and olanzapine third. These three drugs were the only ones to show clear efficacy advantages over haloperidol. The magnitude of differences was again small (but potentially substantial enough to be clinically important)13 and must be weighed against the very different adverse effect profiles associated with individual antipsychotics. A 2019 network meta- analysis of 32 antipsychotics14 ranked amisulpride as the most effective drug for positive symptoms and clozapine as the best for both negative symptoms and overall symptom improvement. Olanzapine and risperidone were also highly ranked for positive symptom response. The greatest (beneficial) effect on depressive symptoms was seen with sulpiride, clozapine, amisulpride, olanzapine and the dopamine partial agonists, perhaps reflecting the relative absence of neuroleptic-induced dysphoria common to most FGAs.15 In the longer term, olanzapine may have advantages over some other antipsychotics.16 There was a tendency for more recently introduced drugs to have a lower estimated efficacy – a phenomenon that derives from the substantial increase in placebo response since 1970.17 Clozapine is clearly the drug of choice in refractory schizophrenia,18 although bizarrely, this is not a universal finding,19 probably because of the biased nature and quality of many

active–comparator trials.20,21 Both FGAs and SGAs are associated with a number of adverse effects. These include weight gain, dyslipidaemia, increases in plasma glucose/diabetes,22,23 hyperprolactinaemia, hip fracture,24 sexual dysfunction, EPS including neuroleptic malignant syndrome,25 anticholinergic effects, venous thromboembolism (VTE),26 sedation and postural hypotension. The exact profile is drug specific (see individual sections on

4 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 specific adverse effects), although comparative data are not robust27 (see large-scale meta-analyses13,28 for rankings of some adverse-effect risks). Adverse effects are a common reason for treatment discontinuation,29 particularly when efficacy is poor.13 Patients do not always spontaneously report adverse effects, however,30 and psychiatrists' views of the prevalence and importance of adverse effects differ markedly from patient experience.31 Systematic enquiry, together with a physical examination and appropriate biochemical tests, is the only way accurately to assess their presence and severity or perceived severity. Patient-completed checklists such as the Glasgow Antipsychotic Side-effect Scale (GASS)32 can be a useful first step in this process. The clinician-completed Antipsychotic Non-Neurological Side-Effects Rating Scale facilitates more detailed and comprehensive assessment.33 Non-adherence to antipsychotic treatment is common and here the guaranteed medication delivery associated with depot/long-acting injectable antipsychotic preparations (LAIs) is unequivocally advantageous. In comparison with oral antipsychotics, there is strong evidence that depots are associated with a reduced risk of relapse and rehospitalisation,34–36 although randomised controlled trials (RCTs) do not always reflect this difference.37 Any logical assessment of the benefits of LAIs and the damage caused by relapse would conclude that LAIs should be first--line treatments, rather than reserved for those who have already relapsed on oral medication. Moreover, the wider use of SGA LAIs has to some extent changed the image of depots, which were sometimes perceived as punishments for miscreant patients. Their tolerability advantage probably relates partly to the better definition of their therapeutic dose range, meaning that the optimal dose is more likely to be prescribed (compare aripiprazole, with a licensed dose 300mg or 400mg/month, with flupentixol, which has a licensed dose in the UK of 50mg every 4 weeks to 400mg/week). The optimal dose of flupentixol is around 40mg every 2 weeks28 – just 5% of the maximum allowed. As already mentioned, for patients whose symptoms have not responded sufficiently to adequate, sequential trials of two or more antipsychotic drugs, clozapine is the most effective treatment.38–40 Its use in these circumstances is recommended by NICE3 and probably every schizophrenia guideline besides. The biological basis for the superior efficacy of clozapine is uncertain.41 Olanzapine should probably be one of the two drugs used before clozapine.10,42 A case might also be made for a trial of amisulpride: it has a uniformly high ranking in meta-analyses and one trial found continuation with amisulpride to be as effective as switching to olanzapine.43 This same trial also suggested clozapine might be best placed as the second drug used, given that switching provided no benefit over continuing with the first prescribed drug. This chapter covers the treatment of schizophrenia with antipsychotic drugs, the relative adverse effect profile of these drugs and how adverse effects can be managed.

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