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Schizophrenia and related psychoses CHAPTER 1 First-generation antipsychotics – place in therapy Nomenclature First-generation (‘typical’) and second-generation (‘atypical’) antipsychotic medications are not categorically differentiated. Drugs in both groups differ substantially in pharmacological and adverse-effect profiles and there is some overlap between the two groups in pharmacological characteristics. FGA medications were introduced before 1990 and tend to be associated with acute EPS, hyperprolactinaemia and, in the longer term, TD. It might be expected that these adverse effects are less likely or absent with SGA medications (introduced after 1990), although in practice most SGAs show dose- related EPS, some induce hyperprolactinaemia (some to a greater extent than FGAs) and all will give rise to TD, albeit at a lower incidence than FGAs. SGA medications tend to be associated with metabolic and cardiac complications,1–3 although this is not true of all SGAs and it is true of some FGAs. To complicate matters further, it has been suggested that the therapeutic and adverse effects of FGAs can be separated by careful dosing.4 That is, FGAs can be indistinguishable from SGAs if used in small enough doses (there is much evidence to the contrary).5–7 Given these observations, it seems unwise and unhelpful to consider so-called FGAs and SGAs as distinct groups of drugs. Perhaps the essential difference between the two groups is the size of the therapeutic index in relation to acute EPS. For instance, haloperidol has an extremely narrow range of doses at which it is effective but does not cause EPSEs (perhaps 4.0–4.5mg/day) whereas olanzapine has a wide range of therapeutic doses (5–40mg/day) at which it does not generally cause such adverse effects. The use of NbN1,2 (for which there is a free application for smartphones and other devices) obviates the need for classification into an FGA or SGA and describes individual drug by their pharmacological activity. NbN is certainly a useful alternative to standard classifications, but one possible limitation is that it preselects specific pharmacological features to create categories while ignoring others, based on the opinion of experts that these features are essential to drug action (despite exact mechanisms of action being unknown). In 2023, a different approach based on in vitro binding profiles was proposed.3 Four clusters of effects were identified, one with high affinity for muscarinic receptors (e.g. olanzapine and quetiapine), one with relatively low antagonism of the dopamine D2 receptor (e.g. the partial agonists and lurasidone), one with serotonergic antagonism (e.g. risperidone) and one with relatively pure dopaminergic antagonism (e.g. amisulpride). These clusters mapped to adverse--effect profiles with greater accuracy than the other classification systems. One possible disadvantage of this so-called data-driven approach is that all receptors are assigned an equal level of importance regardless of their magnitude of impact in producing clinically relevant effects. The

wider use of NbN or the data-driven approach will undoubtedly improve understanding of individual drug effects and perhaps forestall future redundant categorisation. Role of older antipsychotics FGAs still play an important role in schizophrenia. For example, haloperidol is a frequent choice for ‘when necessary’ medication and depot preparations of haloperidol, zuclopenthixol and flupentixol are still commonly prescribed. FGAs can offer a valid

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