# 04 - Extrapyramidal effects

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© SPMM Course 3. Antipsychotics - adverse effects Extrapyramidal effects Acute extrapyramidal syndromes such as acute dystonia, akathisia and parkinsonism are noted with high potency drugs more than low-potency drugs. Tardive dyskinesia and dystonia, perioral tremor (rabbit syndrome) are chronic late side effects. PET studies have indicated that 60%–80% occupation of D2 receptors is associated with antipsychotic efficacy. Higher occupancy levels are associated with an increased risk of acute extrapyramidal symptoms as well as hyperprolactinemia from the blocking of D2 receptors on anterior pituitary mammotrophic cells that normally are tonically inhibited by dopamine produced in the hypothalamic arcuate nucleus. Antipsychotic drugs which have the propensity to induce Parkinsonism (trifluoperazine, chlorpromazine, raclopride, haloperidol, fluphenazine, risperidone) bind more tightly than the endogenous ligand dopamine to D2, while the drugs with low Parkinsonism-inducing propensity (quetiapine, clozapine etc) bind more loosely than dopamine to D2 receptors. Compared to the tightly bound antipsychotic drugs, the loosely bound ones are weaker in potency and thus require higher doses to be clinically effective, but can be titrated faster. These loosely-bound drugs may also dissociate from the D2 receptor more rapidly and could lead to clinical relapse somewhat earlier than the traditional tightly bound antipsychotic drugs (though ths does not seem to be the case for clozapine). Drug-induced parkinsonism is seen in 15-20% of patients treated with antipsychotics, seen within 90 days of treatment (5 to 90) and is characterized by muscle stiffness, cogwheel rigidity, shuffling gait, stooped posture, and drooling. The pill-rolling tremor of idiopathic Parkinsonism is not seen in drug-induced EPSEs - but a regular coarse tremor is seen. Elderly and female are under higher risk. Low potency drugs and those with higher anticholinergic effects cause less EPSEs. It is thought that higher than 80% receptor occupancy of brain D2 by antipsychotics can cause EPSEs. Atypical drugs cause low EPSEs probably due to anticholinergic effects, HT2A antagonism or less avidity of binding i.e. hit and run profile especially for clozapine and quetiapine. Anticholinergics can be used for short period of up to 6 weeks to treat the parkinsonian symptoms. As tolerance can develop for EPSE, the anticholinergics should be withdrawn after 4 to 6 weeks; also, longer chronic anticholinergic prescription increases the risk of TD. The rabbit syndrome is a tremor affecting the lips and perioral muscles and occurs late in the course of treatment.

© SPMM Course Dystonias are brief or prolonged contractions of specific groups of muscles resulting in symptoms such as oculogyric crises, tongue protrusion, trismus, torticollis, blepharospasm. Rarely pharyngeal dystonia can occur resulting in dysarthria, dysphagia, and even respiratory choking. Dystonias occur early in treatment course and can reduce compliance. It is often seen in younger men receiving a high dose of high-potency medications. It is more common with IM administration. Dopaminergic hyperactivity in the basal ganglia occurring when plasma

levels fluctuate may be the mechanism behind dystonias. Dystonias show spontaneous fluctuations, response to reassurance and to anticholinergic drugs. Akathisia includes both subjective and objective - feelings and signs of restlessness. (Possibly due to higher D2 occupancy in striatum). Patients may exhibit inability to relax, jitteriness, pacing, rocking with alternation of sitting and standing. Akathisia can be caused by not only neuroleptics but also antidepressants and sympathomimetics. Dose reduction, changing the drug or adding beta blocker/anticholinergic drugs or benzodiazepines or cyproheptadine are recommended. Akathisia may be associated with an increase in absconsion, suicides and violence if left undiagnosed and untreated in some cases. Tardive dyskinesia is a late side effect occurring in nearly 25% patients usually only after (at least 6 months) 1 – 2 years of treatment. It presents as abnormal, involuntary, irregular choreoathetotic movements of the muscles of the head, limbs, and trunk. Perioral movements are the most common. In some serious cases, patients may have breathing and swallowing muscles involved leading to aerophagia and grunting. TD is exacerbated by stress but is absent during sleep. The absence of insight about the movement disorder is striking in patients. Most cases remit spontaneously. Elderly have a poor spontaneous resolution. Tardive dyskinesia is less likely to remit in elderly patients than in young patients, however. Clozapine can reduce the risk and also treat TD. Dose reduction, withdrawal of the drug, switch to newer atypicals or adding clonazepam can be considered. Neuroleptic Malignant Syndrome Can occur at any time during treatment with neuroleptics RISK FACTORS FOR TARDIVE DYSKINESIA Female gender Elderly Diabetics Previous brain damage Affective illness rather than pure psychotic disorder Children Learning disabled Afro-Caribbean race Long term co-prescription of anticholinergics Frequent drug holidays – will lead to high dose prescription with each relapse

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