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Pharmacotherapy/Psychotherapy Research

Assessment of side effects

This presentation will focus on selecting and assessing adverse events and side effects of medications in clinical drug trials. The presentation will cover a method of assessing extrapyramidalside effects and other consequences of psychotropic medications.

Clinical drug trials

Determining safety and efficacy of new medications

Efficacy – how well the drug works in a clinical trial

Effectiveness – how well the drug works in practice – depends on tolerance and therefore adverse effects and side effects

The process of determining safety and efficacy of new drugs

Preclinical studies – test tube and animal experiments – determine treatment potential (pharmacodynamics) and toxicity information

Phase 0 – 'first in human' trials, microdosing studies, pharmacodynamic (P-D) and pharmacokinetic (P-K) information

Phase I – testing in healthy volunteers – safety, tolerability, P-K, P-D information

Phase II – efficacy studies – small numbers – IIA dosing requirements, IIB efficacy assessments
Phase III – large scale, multi-centre, randomized allocation, placebo or comparator trials – efficacy and safety and tolerability information
Phase IV – post marketing surveillance trails – efficacy, safety, tolerability, detect rare adverse events
Phase V – translational research – how new treatment or drug in integrated into clinical practice

Adverse Events

Major negative outcomes – death, hospitalization, impairment, needs intervention – judged to be drug-related

Side Effects

Less serious undesirable effects of drug that will affect tolerability

Side Effects – Classification of Causes

Pharmacodynamic

Effect on receptors – therapeutic effect on brain or other organs
Pharmacodynamic interactions – when two or more drugs influence the end organ receptor – serotonin syndrome due to overstimulation of brain 5HT by SSRIs, MAOIs and synthetic opioids (Tramal)

Pharmacokinetic

Absorption

Most psychotropic drugs are lipophilic and are absorbed well from small intestine

Distribution

Most highly bound to plasma proteins (so watch available levels if displaced by other medications), lipophilic - pass across blood-brain barrier, enter fat stores and released slowly, large volumes of distribution

Metabolism

Mainly liver - first pass metabolism can vary, CYP450 enzyme metabolism – inducer (carbamazepine) and inhibitor drugs and drug interactions, rate of CYP metabolism – genetic testing – 'personalized medicine', active and inactive metabolites (measurement of parent drug level may not be reliable guide)

Excretion

Usually in the kidney, but some drugs excreted in bile and re-absorbed (chlorpromazine)

Renal and liver function needs to be considered in dosing decisions and presence of side effects

Lithium excreted in kidney and reabsorbed in renal tubule and competes with sodium – when sodium depleted (diuretics) lithium extra reabsorbtion and toxicity

Measurement of circulating drug concentrations

A standard dose of a psychotropic (nortriptyline TCA) can have a ten-fold difference in plasma level in different individuals – so measure plasma levels?

But plasma levels do not predict therapeutic response – may better inform on toxicity and side effects (peak levels)

Pharmacodynamic measures

PET receptor occupancy – holds promise as a method for determining pharmacodynamic effect of drug (eg. dopamine (D2) occupancy) – but patients with same occupancy may or may not respond to dopamine blocking drugs

Pharmacogenetics in psychotropic medication

Polymorphic (allelic) variation in DNA produces proteins that interact in different ways to psychotropic drugs – causing variability in treatment response and development of side effects

Genetic variation in CYP metabolic enzymes – alter blood levels and brain exposure to drugs – mutation in gene for CYP2D6 associated with development of tardivedyskinesia

Alleles associated with decreased expression of 5HT transporter linked with poor response to SSRIs

Treatment response to clozapine linked to specific alleles of 5HT receptor

Weight gain with antipsychotics associated with allele of 5 HT2c receptor

Future applications of genetic typing for individuals to predict treatment response, dosing decisions and development of side effects

Special populations where side effects may be more common

Children, elderly (>65 years), pregnancy and breast-feeding

Psychotropic medications

Antipsychotics

First generation antipsychotics – low potency drugs
Phenothiazines – chlorpromazine
Piperidines – thioridazine
Sedation (antihistamine H1), dry mouth, constipation (muscarinicanticholinergic), postural hypotension (alpha 1 antagonist), low extrapyramidal syndrome effects (EPS)

First generation antipsychotics – high potency drugs
Piperazines – trifluoperazine and fluphenazine
Thioxanthenes (flupenthixol and clopenthixol) and butyrophones (haloperidol)
Highly selective D2 antagonists, low sedation, high EPS

Atypical antipsychotics

Benzamines – amisulpride
Highly selective D2 antagonist with low EPS and low sedation, but prolactin increase

5HT2 – D2 receptor antagonists – clozapine the prototype
Also antihistamine (sedation and weight gain), alpha 1 adrenergic (postural hypotension), muscarinic cholinergic stimulation (salivation), leucopenia, low EPS

Others in this Class

Risperidone – potent 5HT2 and D2 blocker, low sedation, higher EPS and prolactin increase

Olanzapine – less selective D2, but histamine and cholinergic antagonism – sedative, weight gain, low EPS

Quetiapine – weak D2 antagonism, modest 5HT2 blocker – sedative, low EPS

Aripiprazole – partial D2 antagonist and 5HT2 blocker – little sedation, insomnia, gastrointestinal side effects, low weight gain

Antipsychotic Side Effects

Anti-dopaminergicand anticholinergic

Other adverse and side effects

Cardiac arrhythmias, seizures (clozapine), myocarditis and myopathy (clozapine), weight gain, diabetes, amenorrhoea, galactorrhoea, hypothermia, cataracts, photosensitivity

Extrapyramidal Syndrome Effects

Action of dopamine antagonism on basal ganglia
Atypical antipsychotics have greater effect on mesolimbic and mesocortical pathways, less direct effect on basal ganglia dopamine pathways – so less EPS

Types of EPS

1. Acute dystonia
2. Akathisia
3. Parkinsonian syndrome
4. Tardivedyskinesia
5. Tardivedystonia
Neuroleptic malignant syndrome

Physical examination for EPS (demonstration)

Assessing Side Effects

Symptom problem check lists – cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, hematopoietic, skin, sexual, genitourinary, hormonal

Routine physical examination, BP, pulse, ECG, eyes (double vision, cataracts)
Blood and other tests – electrolytes, RFTs, LFTs, FBC, micro urine

Metabolic syndrome – definition

Overweight-obese, excess waist circumference (ethnic variations noted)
Hyperglycemia – Type II diabetes
Hypertension – >135/85
Hyperlipidemia – especially low HDL and raised triglycerides
Smoking
Physical inactivity
Poor diet (high fat, high sugar foods and drinks, low amounts vegetables and fruit)

Antipsychotic Metabolic Syndrome

All antipsychotics, but especially atypical antipsychotics
50% of patients with chronic psychosis
2-5 times more common than general population

Tendency to cause weight gain – a guide to risk of metabolic syndrome

High risk – clozapine, olanzapine, quetiapine

Moderate risk – risperidone, palperidone, amisulpride

Low risk – aripiprazole, ziprasidone

Antipsychotic medications – monitoring side effects

Each visit – weight and waist measurement, any adverse events, smoking status, alcohol and illicit drug use
Each six months – EPS examination
Each six months for 'high risk' drugs – BP, fasting blood sugar and lipids
Each year for 'moderate and low risk' drugs – BP, fasting blood sugar and lipids
Each year – check for sexual, menstrual and breast symptoms

Antidepressant Safety Guidelines
(Dodd et al. ANZJP 2011, 45:712-725)

Monitor side effects in major depressive disorder patients on antidepressants

Antidepressant side effect symptom checklist
Suicide risk
Obesity and metabolic syndrome
Cardiovascular status – BP (des-venlafaxine, TCAs, MAOIs), ECG (TCAs)
Hyponatraemia
Bone mineral density (SSRIs)

Re-medicalization of psychotropic drug prescribing?

Thank you!