11 - 41_Basic_Pharmacology

01 - 1. Historical overview

1. Historical overview

1. Historical overview

 In 1915, Macht and Mora coined the term "psychopharmacology" when studying opioid alkaloids on rat behavior in a circular maze. In 1931 Sen & Bose, Indian physicians from Calcutta, reported on the antipsychotic properties of the plant Rauwolfia serpentine. Reserpine was rediscovered by Kline in 1954. In 1949, Cade in Australia discovered the use of lithium compounds in mania, initially on the basis of a presumed relationship between urate metabolism and mania. Lithium urate was prescribed to promote the solubility of uric acid. Later he noted that lithium ion itself had calming properties even in healthy controls. Between 1950 & 1952 presurgical antihistamine chlorpromazine was shown to have antipsychotic effects independently by Delay and Deniker's team, and Charpentier from Rhône-Poulenc in France. In 1955 Delay coined the term neuroleptic. The first true antidepressant was discovered in 1952. Mood lifting properties of Iproniazid, an anti-tuberculosis treatment, led to the discovery of the antidepressant class. But hypertensive reactions precluded the large-scale use of iproniazid. Imipramine, which was manufactured as chlorpromazine derivative, came to market soon after. The first benzodiazepine, chlordiazepoxide (Librium) was discovered serendipitously by the Austrian scientist Leo Sternbach in 1954. Kuhn (1958) discovered that among the various different psychiatric disturbances 'endogenous' depression responded best to imipramine. In 1961, second TCA amitriptyline was introduced. In 1958, Janssen synthesised butyrophenone haloperidol from pethidine. Wide scale use of antipsychotics started from this time. Antipsychotics came to be known as major tranquilizers while barbiturates and benzodiazepines were called minor tranquilizers. Large scale hospital discharges and deinstitutionalization started. 1963 Cheese reaction was proposed to be the mechanism for MAOI associated hypertension by Blackwell.

  Janssen synthesized an atypical agent risperidone in 1989.

 Carlssen synthesized purpose made SSRI Zimeldine – but this was withdrawn due to the incidence of hypersensitivity syndrome and demyelinating disease that followed its use. In 1970s, Fluoxetine was tested as a noradrenaline reuptake inhibitor but was discarded as it had a poor activity in this regard. Later it was rediscovered as serotonin reuptake inhibitor, reaching the market in 1987. Kane et al. 1988 rediscovered clozapine via a multicentre randomized design comparing chlorpromazine vs. clozapine in 'treatment resistant' schizophrenia. 4% showed response to chlorpromazine while 30% showed response to clozapine. 1990s 'Prozac era' – widescale antidepressant prescription started Reappraisal of suicides associated with

antidepressant treatment – ‘black box warning’ issued for prescribing antidepressants to adolescents and children. CATIE study results published in 2005 – reappraisal of the usefulness of atypical and typical antipsychotics. CuTLASS study from UK follows with a demonstration of no apparent economic gain from atypicals.

02 - 2. Classification of psychotropics

2. Classification of psychotropics

Chemical structure Psychotropics ANTIPSYCHOTICS Aliphatic phenothiazines Chlorpromazine, Promazine, Triflupromazine Piperidine derivatives Thioridazine Piperazine derivatives Trifluoperazine, Fluphenazine, Perphenazine, Thioridazine Butyrophenones Haloperidol, Droperidol Thioxanthenes Thiothixene, Flupenthixol, Zuclopenthixol Dihydroindoles Molindone Diphenylbutylpiperidine Pimozide (long t1/2) Dibenzoxapine Loxapine Benzisoxazole derivative Risperidone Substituted benzamides Amisulpride, Sulpiride Dibenzodiazepine Clozapine Dibenzothiazepine Quetiapine Thienobenzodiazepine Olanzapine Benzisothiazole Ziprasidone Arylpiperidylindole (quinolone) Aripiprazole ANTIDEPRESSANTS Tertiary amines Imipramine, Amitriptyline, Clomipramine, Dosulepin, Trimipramine (also Venlafaxine) Secondary amines [more potent; less sedating; more noradrenergic, less antihistaminic or anticholinergic than tertiary] Desipramine, Amoxapine, Nortriptyline and Protriptyline (also Duloxetine) Hydrazine derivatives Phenelzine, Isocarboxazid (greater hepatotoxicity than Tranylcypromine, a non hydrazine compound) Aminoketone Bupropion (amphetamine-like) OTHER PSYCHOTROPICS Azaspironedecanedione Buspirone Triazolopyridine Trazodone, Nefazodone. Imidazopyridine Zolpidem Pyrazolopyrimidine Zaleplon Cyclopyrrolone Zopiclone Benzothiazolyl piperazine Ziprasidone

03 - Novel agents in the making

Novel agents in the making

© SPMM Course Classification by mechanisms of action SSRIs Citalopram, Paroxetine, Fluoxetine, Sertraline and Fluvoxamine, S enantiomer of citalopram

- Escitalopram SNRIs – serotonin and noradrenaline reuptake inhibitor Venlafaxine, Milnacipran, Duloxetine, Sibutramine NARI – Noradrenaline reuptake inhibitor – Reboxetine NDDI – Noradrenaline Dopamine DisInhibitor - Agomelatine NaSSA – Noradrenergic and specific serotonergic antagonist – Mirtazapine and Mianserin DARI – Dopamine reuptake inhibitor - Bupropion RIMA – reversible inhibitor of Monoamine A oxidase - Moclobemide SARI – serotonin antagonist and reuptake inhibitors – Nefazodone, Trazodone.

Novel agents in the making Xanomeline underwent phase 3 trials as a treatment option for schizophrenia. It acts via M1/M4 agonism Xanomeline showed a trend toward improving cognitive function in Alzheimer’s, and produced robust and dose-dependent reductions in psychotic symptoms in AD. In schizophrenia, early trials showed efficacy in both the positive and the negative symptoms along with improvements in verbal learning and short-term memory but, a high degree of gastrointestinal side effects were observed. Ketamine is a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist that has shown rapid antidepressant effects in treatment-resistant depression. Large scale trials are being undertaken currently. Pomaglumetad methionil (LY2140023 monohydrate), a metabotropic glutamate receptor 2/3 agonist, appeared to be a promising agent for sometime as initial phase 2 studies showed promising efficacy against positive and negative symptoms when used as an add-on therapy in schizophrenia. But this result was not replicated in a later study, mostly due to high placebo response. It is devoid of affinity for dopamine receptors.

04 - 3. The principles of rational prescribing of

3. The principles of rational prescribing of psychotropics

© SPMM Course 3. The principles of rational prescribing of psychotropics Watchful waiting: When treating conditions such as depression and anxiety, NICE recommends watchful waiting before pharmacological interventions. Start-low go slow: Psychotropic medications should be prescribed at the lowest possible dose and for the minimum duration possible. If the expected improvement does not occur, the formulation and the management plan must be revised. Therapeutic monitoring: Many psychotropics have dose-dependent therapeutic and side effects. Plasma monitoring can be useful in some circumstances (see therapeutic window phenomenon discussed later) Metabolic monitoring: Metabolic side-effects arguably contribute to more days of life lost than any other adverse effects when taking psychotropics. Various classes of psychotropics have specific recommendations as to the frequency and extent of metabolic monitoring. Response assessment: A good follow-up schedule is essential to monitor the effect of prescribed psychotropics. Without this, the purpose of pharmacological treatment will fail. Avoiding polypharmacy: Most national guidelines explicitly recommend avoiding the combination of psychotropic agents, especially antipsychotics. Informed consent: When prescribing, it is imperative that pros and cons of a treatment are discussed in advance to enable the patient to make an informed decision regarding the treatments offered. Patient choice: Guidelines such as NICE recommends that patients must be supported to make the final choice of a specific psychotropic drug for an indication (e.g. antipsychotics for psychosis) from various options provided by the psychiatrist. Off-label use: While off-label use of psychotropics for uncommon, non-specific indications is not recommended; this practice is not illegal per se in most countries. Such practices often have only flimsy or no evidence-based support. The prescriber must explain to the patient if the medication is being used outside its licensed indications and provide the available evidence to demonstrate its effectiveness. CHEMISTRY & STORAGE

Drugs exposed to moisture and light can gain moisture quickly – reducing the availability of active excipients. This is termed as hygrophilicity. Some drugs are extremely sensitive to environmental moisture to such an extent that they will turn from crystalline states into pastes or liquids if left in contact with moist air even for a short period of time. A good example of this type of deliquescent material is Sodium Valproate. This property is called as deliquescence.

© SPMM Course Long-term prescriptions: When treating chronic illnesses, relevant local & national guidelines should be followed. Information about which medications worked before and which did not should be noted, in addition to noting the adverse effects produced by each of them.

05 - 4. Placebo effect

4. Placebo effect

© SPMM Course 4. Placebo effect Placebo is any intervention deliberately used for non-specific psychological or psychophysiological treatment effect. Placebo effect, as defined in research trials, includes any difference in outcome between a placebo-treated group and an untreated control group in an unbiased experiment (Ernst 2001). Placebos could be pharmacologically active or inert substances, most commonly the latter. An ‘active placebo’ has some activity inherently, but not against the treated condition. The term placebo literally translates in Latin meaning ‘to please’. It was coined by an anaesthetist Beecher in 1955. When a substance administered for placebo effects produces prominent side-effects, it is known as a ‘nocebo’. The term ‘nocebo effect’ (Latin: ‘I shall harm’) refers to the negative consequences, adverse reactions and intolerance resulting from the administration of a placebo. Nocebo effects are usually non-specific e.g. headache and nausea. Placebo sag is a term used to refer to decrease in placebo effect with repeated or chronic administration of placebo drugs. The placebo effect may be disproportionately large for non-blinded therapies potentially resulting in what has been called the efficacy paradox. Placebos work best for pain, disorders of autonomic sensation, and disorders of factors under neurohumoral control e.g. nausea, blood pressure, and bronchial asthma. Psychiatric disorders such as depression, anxiety and phobias show good placebo response. In depressive illness, the response rate varies from 25 to 60%, in mania it is as high as 25% and in schizophrenia it may vary from 25 to 50%, depending upon the criterion of improvement that is used and other factors. In panic disorder, placebo response rates of up to 70% are seen. More chronically ill patients show lower placebo response rates. Placebos fail in hereditary degenerative disorders, toxic and metabolic syndromes or vascular events. Placebo effects are not unique to placebo preparations; they are seen with active drugs too. e.g. a substantial proportion of patients responding to analgesics or antidepressants do so due to the placebo effect. Hence, the net effect of a given drug is thus the sum of the drug's pharmacological effects and the placebo effect. Physiological changes in opioids and GABA have been proposed to explain some aspects of placebo action; this neuropeptide hypothesis holds good for placebo analgesia, but not proven to operate in other conditions e.g. depression. Three factors are necessary for placebo action: the nature of the disease treated and the nature of the dynamic relationship between patient and doctor, patients’ expectations and experience with treatment in the past. Gender, suggestibility scores, and IQ do not affect placebo effect consistently.

© SPMM Course Placebos are more effective for clinical than experimentally induced conditions. Placebos work better for severe than mild pain, but mildly depressed patients respond well than severely depressed ones. In studies of depression and schizophrenia the difference in improvement in the group of patients on active treatment compared with the group on placebo increases gradually, with little difference until about 2 weeks of treatment and the full difference

developing by 6 weeks and it increases progressively for several months. Those who respond to a placebo for one condition, when treated by one doctor, will not show same placebo response for another condition or another doctor. Hence, there are no homogeneous placebo reactors in the population. This view is furthered by the demonstration that the use of placebo ‘run-in’ approach in antidepressant trials, wherein ‘placebo reactors’ are eliminated before the trial commences, does not actually lower the placebo response rate or increase the drug–placebo difference to a great extent. But such procedures reduce generalisability and pragmatic nature of these trials as placebo responders may be most likely to benefit from a biologically active treatment, and their exclusion makes any estimate too conservative. A placebo can be a procedure and not a medication e.g. sham ECT, and sham surgeries with the only skin incision. The placebo response is higher in trials with more than 2 arms compared to those with two arms only (placebo vs. active arms). In a three-armed trial, participants are aware that they have 2 /3 chance of receiving active treatment compared to ½ chance in 2 armed study – hence there is a higher placebo response. People have individual traits that predispose them to be more or less responsive to certain stimuli; the interaction between the learned associations of the clinical situation and the person’s particular biology produces a response. Placebo analgesia may be associated with decreased beta-adrenergic activity of the heart as measured by decreased heart rate and low-frequency heart rate variability Capsules are perceived to be stronger than tablets, producing more placebo effects. Larger pills have stronger placebo effect than smaller pills. The number of pills also influences the perception of pill strength. Multiple pills have stronger placebo effect than single pills. Anxiety symptoms responded better to green tablets and depressive symptoms responded better to yellow tablets. These are examples of the relative potency of medication varying with pill colour (Schapira et al. 1970). Injections elicit a stronger placebo effect than oral medications. Surgery is likely better than the others in terms of eliciting placebo effects. Why does a placebo work?

1. Natural remission theory states that the disorders for which placebo works are inherently episodic (i.e. natural cycles show periods of remission and relapse). Hence even without treatment an improvement would have occurred, and placebo use is merely coincident.
2. Measurement regression: When a continuous variable is measured repeatedly in a sample, with each subsequent measurement the mean of the sample will move from extreme values and become closer to the population mean, the central value. This might explain why there is an apparent placebo response in control groups.
3. Conditioning theory: Placebo is in a way a behavioural intervention. Patients, who have learnt that receiving a medication will improve symptoms, will be showing a conditioned response of improvement when a placebo is administered. Learned associations producing placebo effects can be acquired through conditioning, especially for immune or endocrine conditions. According to classical conditioning models of placebo effects active medications are Unconditioned Stimuli and the vehicles in which they are delivered (i.e., the pills, capsules, syringes, etc.) are Conditioned Stimuli. The medical treatments that people experience during their lives constitute conditioning trials, during which the vehicles are paired with their active ingredients leading to the unconditioned response of therapeutic benefits initially. These repeated pairings endow the pills, capsules, and injections with the capacity to evoke therapeutic effects as Conditioned Responses later on. During placebo treatment, the belief of the patient in being treated may result in

selective attention to symptom improvement and expectation. The momentary experience of symptom improvement may then act as a reward and positively reinforce preceding changes of autonomic function. Thus, visceral learning due to a mechanism similar to operant conditioning may occur, in which the reward is internally provided Placebo responses are mediated by conditioning when unconscious physiological functions, such as hormonal secretion, are involved, whereas they are mediated by expectation when conscious physiological processes, such as pain and motor performance, come into play, although a conditioning procedure is performed.

4. The role of endogenous opioids: Endogenous opioids (e.g. endorphins) play a significant role in mediating placebo-induced analgesia. Interestingly, placebo-induced analgesia is partially reversed by administering the opioid antagonist naloxone. Dopamine reward system is being increasingly implicated in placebo effects in psychotropic research. The nature of placebo response in depression is compared with the antidepressant-induced response in depression. Placebo response starts abruptly, occurs early in treatment and is less likely to persist (Quitkin et al., 1991). But the antidepressant response is often gradual, occurs later and is more likely to persist. But the neurobiological correlates of the responses may not be truly

 different as shown by Mayberg et al. (2002). Mayberg et al. (2002) observed that the patients in their study whose depression relented after treatment with either fluoxetine or placebo had nearly identical positron emission tomography (PET) brain scans. The ACC is an important anatomical component of the dopaminergic as well as an opioid system and has been activated during placebo analgesia.

06 - 5. Drug approval

5. Drug approval

© SPMM Course 5. Drug approval Any drug must undergo the following steps before approval is granted by regulatory agencies such as FDA in the US and MHRA in the UK.

1. Preclinical Animal Studies: The pathway a drug must undergo before approval and marketing start with animal studies where the molecule is demonstrated to have specific actions. These extensive preclinical animal studies must be carried out at least on two different animal species. Mutagenicity, carcinogenicity and organ system toxicity are studies at this phase.
2. Human trials – volunteers phase 1: (safety) An investigational new drug then enters human trials. The first phase consists of determining if the drug is safe for human subjects. It is administered to a small group of volunteers and safety; tolerability and pharmacokinetics of the drug are ascertained. They are usually open or uncontrolled studies.
3. Human trials – patients phase 2: (effectiveness) In phase 2 effectiveness is studied in hundreds of patients with target disease in comparison to placebo to see if it works at all against the disease. The main methods are controlled trails or small randomized controlled trials.
4. Human trials – patients phase 3: (superiority or equivalence to standard looking for comparative efficacy) and tolerance profile) In phase 3 the drug undergoes extensive doubleblind RCT to determine how well does it work and what are the common side effects.
5. Human trials – post-marketing surveillance phase 4: Phase 4 takes place if all the previous phases are successfully crossed – the drug undergoes an approval process by regulatory bodies and post-marketing surveillance ensues. Less common side effects, which sometimes could lead to drug withdrawal, can be picked up when large scale prescribing takes place during postmarketing surveillance observations. Psychotropic Drugs Adverse effects detected by post marketing surveillance
6. Nefazadone Hepatotoxicity
7. Droperidol, Thioridazine QT prolongation on ECG
8. Sertindole Sudden cardiac death
9. Thalidomide (analgesic) Phocomelia
10. Nomifensine Hepatotoxicity
11. Zimeldine Hypersensitivity reactions and Guillain-Barre syndrome
12. Remoxipiride(sulpiride group) Aplastic Anaemia
13. Mianserin Blood dyscrasias
14. MAOIs Cheese reactions

15. Clozapine Agranulocytosis

07 - 6. Medication adherence

6. Medication adherence

08 - Adherence measurement tools

Adherence measurement tools

© SPMM Course 6. Medication adherence Compliance is defined as the extent to which a person’s behaviour coincides with medical advice. o Implies sole patient’s responsibility o Criticized as paternalistic. Adherence includes the concept of patient choice: both clinician and patient share the responsibility for adherence. o In most research, definitions for adherence are usually dichotomous, but adherence is rarely an all-or-nothing phenomenon. Concordance is based on the notion that the therapeutic alliance between the prescriber and patient is a negotiation process, with equal respect for both the patient’s and clinician’s agenda Adherence measurement tools Self-report methods: For example, using the Tablet Routines Questionnaire, which assess the daily routines for taking medication and the proportion of drug an individual has missed in the previous week and last month (Scott and Pope, 2002) Pill counts Adherence (%) can be calculated as (number of pills taken ÷ number of pills prescribed) × 100 (Azrin and Teichner, 1998) Electronic methods Electronic devices have been developed which can be attached to the tablet bottle. They record the time and date on every occasion that the bottle is opened Prescription monitoring The frequency of prescription dispensing for an individual can be monitored as a proxy measure of adherence Saliva, plasma and urine assay tests Most objective measures Not available for all psychiatric drugs – expensive, invasive and have limited value in assessing partial adherence, leading to overestimate of adherence to long half-life drugs. Non-adherence rates are reported as 40–60% for antipsychotics, 18–56% for mood stabilizers and 30–97% (median 63%) for antidepressants. Nonadherent patients with schizophrenia are 3.5 times more likely than adherent patients to relapse within 2 years.

09 - Factors affecting adherence

Factors affecting adherence

10 - Improving adherence

Improving adherence

© SPMM Course Factors affecting adherence

 Patients with poor insight may still take medications – accepting label is less important than enhancing awareness of drug effects Dose strength – the relationship between dose strength and adherence is probably curvilinear, with very low doses being associated with poor efficacy and very high doses with excessive side-effects The health belief model of adherence outlines four main belief categories that a patient considers before making a decision regarding prescribed medications:

1. Benefits
2. Costs
3. Susceptibility
4. Secondary benefits of medication and adherence.

Improving adherence Adherence enhancement is possible if the patient's perceptions are altered. Most patient/family directed psychoeducational programmes focus primarily on imparting knowledge without focusing on attitudinal and behavioural change; hence they are largely ineffective in enhancing adherence. Factors with no influence on adherence Factors with no influence on adherence •Age at illness onse •Age at first hospitalization •Sex •Socioeconomic status, •Marital status •Ethnicity Factors that reduce adherence: Factors that reduce adherence: •Asymptomatic stage of illness •Cognitive deficits •Comorbidity – alcohol and substance misuse •Devaluation of medication effects by the physician •Fear of side-effects. •High frequency of daily doses •Homelessness •Lack of insight (most common cause) •Long duration of illness (chronic diseases) •Oral formulations have poorer adherence than depots •Past history of non-adherence •Polypharmacy •Prophylactic or maintenance treatments •Psychopathology of hostility, suspiciousness and disorganization Factors that increase adherence Factors that increase adherence •Presence of family support •Liquid or sublingual forms •High enthusiasm fromclinican •Good patient-clinician relationship •Continued access to clincians

© SPMM Course Cognitive-based interventions target the patient's attitudes and beliefs towards medication to influence the personal construction of the meaning of medication and illness (Zygmunt et al., 2002). Behaviour-modification interventions assume that behaviour is learnt and can be modified. Patients are provided with instructions and strategies (e.g. reminders, selfmonitoring tools, cues and reinforcements) to improve adherence (Zygmunt et al., 2002). Motivational interviewing enables the patient to express personal reasons for and against improving their treatment adherence. Compliance therapy is a brief intervention based on

motivational interviewing and cognitive approaches. In compliance therapy, a patient's ambivalence towards medication is explored initially, followed by a discussion of the consequences of medication cessation. Analogies with chronic physical illness are made, and the pros and cons of medication are considered during the course of treatment.

 Deb, S et a (2008). International guide to prescribing psychotropic medication for the management of problem behaviours in adults with intellectual disabilities. World Psychiatry; 8(3); 181-86 Ernst, E. (2001) Towards a scientific understanding of placebo effects. In Understanding the Placebo Effect in Complementary Medicine. Theory, Practice and Research (ed. D. Peters), pp. 17–30. London: Churchill Livingstone. Ian M Anderson & Ian C Reid. Fundamentals of clinical Psychopharmacology (2nd edition) Kaur H, Mariappan TT, Singh S. Behavior of uptake of moisture by drugs and excipients under accelerated conditions of temperature and humidity in the absence and presence of light Part-III, Various drug substances and excipients. Pharma Technology 2003:52-56 Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, Jerabek PA: The functional neuroanatomy of the placebo effect. Am J Psychiatry 2002; 159:728-737 Oken BS . Placebo effects: clinical aspects and neurobiology (2008), 131, 2812^2823 Patel, M & David, A. Medication adherence: predictive factors and enhancement strategies Psychiatry, 3, 10:41-44. Quitkin, FM et al (1991) Heterogeneity of clinical response during placebo treatment. American Journal of Psychiatry, 148, 193 -196 Rajagopal, S. The placebo effect. Psychiatr Bull 2006 30: 185-188 Sadock, BA & Sadock, VA (ed). Kaplan & Sadock's Comprehensive Textbook of Psychiatry. Lippincott Williams & Wilkins; 8th edition Ter Riet et al (1998) Is placebo analgesia mediated by endogenous opioids? A systematic review. Pain, 76, 273 -275 The use of drugs in Psychiatry; John Cookson, David Taylor and Cornelius Katona. (5th edition) Vallance, AK. Something out of nothing: the placebo effect. Advan. Psychiatr. Treat., July 1, 2006; 12(4): 287 - 296.