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NEUROPSYCHIATRIC ADVERSE EFFECTS OF PSYCHOTROPIC AGENTS: A REVIEW

Introduction

There are several psychotropic agents used to treat different mood disorders possessing many structural and functional characteristics. Some of the psychotropic agents tend to possess neuropsychiatric side effects when used in therapeutic doses. [1]

These agents can be classified based on various features such as the chemical class of the drug, site of action , therapeutic indication. In psychotropic agents we have drugs that have multiple effects eg: antipsychotics such as aripiprazole are effective in schizophrenia, in mania, as antidepressant augmentation treatment in major depressive disorder, as SSRI augmentation treatment in obsessive compulsive disorder, and in the treatment of delirium.[2] Hence here we would we considering the below mentioned classes of importance
in context are: antidepressants, anxiolytics, antipsychotics and stimulants
Psychotropic -related neurotoxic effects can have a vast array of presentations. The risk factors for certain side effects like tardive dyskinesia are - female gender, old age, or existing affective disorders[3]. . Seizures episodes have been reported while being treated with therapeutic doses of most commonly used antidepressants and antipsychotics ranging from approximately 0.1 to approximately 1.5% .[4] Commonly seen neuropsychiatric adverse drug effects upon administration of psychotropic agents are seizures, extrapyramidal effects, neuroleptic malignant syndrome and sleep disorders[1].These have been discussed below in detail. Study publications, case reports and review articles of relevance with respect to the topic, published during 2001–2021 were referred to prepare this review.

Serotonin toxicity

- Serotonin, or 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter that is derived from tryptophan. serotonin modulation is a common mechanism of action for many antidepressants.[5] Stimulation of the postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors from a single or combination of drugs produces serotonin syndrome. Serotonin syndrome is a potentially life-threatening condition caused by the use of serotonergic drugs.[6] This mostly occurs due to the use of the drug for therapy, drug interactions or drug over use. Severe cases are termed as serotonin syndrome, usually follow the co-prescription of drugs that increase serotonergic transmission by different pathways, for example a monoamine oxidase inhibitor (MAOI) and a selective serotonin reuptake inhibitor (SSRI).[7]

Serotonin toxicity manifests as

- Altered mental state such as agitation, excitement, confusion
- neuromuscular hyperactivity which includes tremor, clonus, myoclonus, hyper-reflexia

- autonomic hyperactivity which could manifest as diaphoresis, pyrexia, mydriasis, tachycardia and tachypnoea.

Management consists of discontinuing the causative drug. Supportive treatment must be given. Cyproheptadine is a histamine-1 receptor antagonist with nonspecific 5-HT_{1A} and 5-HT_{2A} antagonistic properties which is widely used as an antidote for serotonin syndrome though supportive evidence are lacking.[5] Patients with abnormal vital signs require admission to a monitored setting, and severe cases must be admitted to the intensive care unit.

Seizures

Most antipsychotics and antidepressants lower the seizure threshold and can cause seizures. Clozapine has higher risk than with other atypical antipsychotics and its greater with tricyclic antidepressants (TCAs) than with SSRIs.[7] Incidence rates for seizures while being treated with therapeutic doses of most commonly used antidepressants and antipsychotics ranges from approximately 0.1 to approximately 1.5% . Seizures triggered by psychotropic drugs are a dose-dependent adverse effect; maprotiline and clomipramine among antidepressants, and chlorpromazine and clozapine among antipsychotics that have a relatively high seizurogenic potential .[8] The drugs with the most propensity to lower seizure threshold included - Imipramine, Bupropion, Clozapine, Olanzapine and Haldol. Relatively safer drugs included Selective Serotonin Reuptake Inhibitors & Selective Norepinephrine Reuptake Inhibitors (SSRI/SNRIs), Risperidone and Seroquel.[9] The most epileptogenic of the conventional antipsychotics is regarded to be Chlorpromazine.[10] Given the impact of psychotropic drugs on the seizure threshold, individual considerations should be given to each patient prior to selecting a psychotropic medication. Depot antipsychotics is to be avoided in patients with epilepsy because the antipsychotics could not be quickly withdrawn if seizures occur.[3]

The medical management of such an event includes a cautious reduction in drug dosage or the substitution of one drug by another member of the same pharmacological group. Anticonvulsants are only sparingly used.

Extrapyramidal syndromes

Extrapyramidal side effects (EPS), are drug-induced movement disorders which are the most common adverse drug effects patients experience from dopamine-receptor blocking agents.[11] The five key extrapyramidal syndromes associated with psychiatric drugs are parkinsonism, akathisia, acute dystonia, tardive dyskinesia and tardive dystonia. The rates of EPS are mostly dependent on the class of medication administered. In a study of first-generation neuroleptics in institutionalised patients with schizophrenia 61.6% were associated with EPS.[12] The mechanism of action is the antagonistic binding of dopaminergic D_2 receptors within the mesolimbic and mesocortical pathways of the brain.[13] The antidopaminergic action in the caudate nucleus and other basal ganglia may also contribute significantly to the occurrence of EPS.

The onset of parkinsonism starts several weeks after the intake of the drug whereas tardive dyskinesia typically starts after months or years of treatment with antipsychotics. Parkinsonism occurs in a triad of tremor, bradykinesia and rigidity. The patient presents with typical symptoms of parkinsonism such as a stooped posture, slow gait with lack of arm swing and a mask-like facial expression. Other features include seborrhoea and sialorrhoea.[14] Reduced

volume and articulation of speech can be seen due to the involvement of laryngeal and pharyngeal muscles. Drug-induced parkinsonism is managed by discontinuing or reducing the dose of the causative medication, switching to an atypical antipsychotic, and administration of medications used for Parkinson disease, including amantadine, antimuscarinic agents, dopamine agonists, and levodopa.[15]

Acute dystonia manifests as contraction of a voluntary muscle to its maximal degree that is sustained and so leads to a postural distortion. The prevalence varies widely from 2% to 90%. Ninety five percent of all cases of acute dystonia appears within 96 hours of starting treatment.[16] The contraction lasts from minutes to hours. The most common site to be affected is the neck though any part of the body could be involved including the tongue, trunk or limbs. Acute dystonia appears usually in the first week after starting or increasing the dose of the antipsychotic and is more common in younger patients and when higher doses of antipsychotics are administered. [16] Tardive dystonia is probably the least well recognized of the extrapyramidal syndromes associated with antipsychotic medication. The main difference between tardive dystonia and acute dystonia is that tardive dystonia presents as a persistent muscle contraction whereas acute dystonia the transient muscle contraction. Tardive dystonia usually commences after years of antipsychotic treatment whereas acute dystonia usually occurs in the first week after starting an antipsychotic, but this difference is not absolute. The pathogenesis of acute dystonia is unclear. As all the antipsychotics bind to D_2 receptors, it is suggested to be the blockage of these receptors in the caudate, putamen, and globus pallidus being partly responsible for causing acute dystonia. Dystonic reactions are rarely life-threatening. The causative drug must be discontinued and manage pain if present. If the causative medication is a first-generation antipsychotic, switching to a second-generation antipsychotic may be considered. Administration of antimuscarinic agents such as benztropine, trihexyphenidyl or administering diphenhydramine may relieve dystonia within minutes. [16] In cases of tardive dystonia, additional therapeutic strategies include administration of benzodiazepine but, benzodiazepines are associated with tolerance and dependence. [17]

Akathisia is a movement disorder generally characterized by subjective feelings of internal restlessness with a compelling urge to move leading to the observation of repetitive movements - such as leg crossing, swinging or persistent shifting from one foot to another. As the clinical presentation of akathisia can be vague and non-specific such as nervousness, inner tension, discomfort, restlessness, itching, and/or an inability to relax, they possess a significant challenge in the clinical practice. These symptoms often tend to be misdiagnosed as persistent anxiety and/or agitation, and a subsequent dose increase is not only ineffective but often exacerbates antipsychotic or selective serotonin reuptake inhibitor (SSRIs)-induced akathisia.[18] The neurotransmitters most specifically linked to akathisia are gamma-aminobutyric acid (GABA) and serotonin. $GABA_A$ exerts an influence on dopamine-dependent signaling and therefore increasing or reducing locomotor activity[18.] Serotonin is involved in motor regulation through the serotonin receptors present in several cortical areas as well as the striatum. Serotonin more specifically regulates the dopaminergic motor function in the nigro-striatal system. The management of akathisia employs strategies like managing dystonia, including stopping or reducing the dosage of the offending medication, switching to a second generation and administering anti-muscarinic agents.

Other therapeutic strategies more specific to akathisia include administration of a beta-blocker, but beta-blockers are contraindicated in those with asthma and peripheral vascular disease.[19]

Tardive dyskinesia consists of involuntary movements that usually start with the orofacial muscles involving the tongue, lips, mouth or face. With failure to diagnose and continued antipsychotic treatment could increase in severity the disorder. Any part of the body can be affected with tardive dyskinesia and there could be a wide range of movements including myoclonic jerks, tics, chorea and dystonia.[20] The pathophysiology of tardive dyskinesia is complex and remains unclear. Multiple neurochemical theories have been proposed to explain this side effect. These theories include - a disturbed balance between dopamine and cholinergic systems; noradrenergic dysfunction; dysfunctions of striatonigral, γ-aminobutyric acid (GABA)ergic neurons; and excitotoxicity.[21] The current management for tardive dyskinesia would be to switch to clozapine, assuming that continuing antipsychotic treatment is required. Tetrabenazine is the only licensed treatment for tardive dyskinesia in the UK but is said to cause depressive symptoms.[22] A wide range of other treatments that lack strong evidence and low success rates include - vitamin E, sodium valproate, essential fatty acids and benzodiazepines. Injection of botulinum toxin for facial dyskinesia have also been reported.[23] According to guidelines of National Institute for Clinical Excellence, 2002[24] in the UK atypical antipsychotics are used as the first line drugs in the treatment of newly diagnosed schizophrenia and patients who are treated with conventional antipsychotics and experience unacceptable EPS should be switched to an atypical agent. Haloperidol is a high-potency first generation antipsychotic drug which has a high propensity to cause EPS. In RCTs that use low-dose low-potency first generation antipsychotics as the comparator there seems to be no significant difference in the incidence of EPS compared to atypical antipsychotics other than clozapine.[25] Second generation antipsychotics does have a lower risk of EPS compared to the first generation drugs.[26] The difference in EPS risk across the antipsychotic drugs is due to the pharmacological differences including the degree of antagonism at dopamine-2 (D_2) receptors, the speed of dissociation from the D_2 receptor, selectivity for limbic versus striatal D_2 receptors, the antimuscarinic potential of the drug and the degree of 5HT2A antagonism.

As most of the medications used for the treatment of EPS comes with side effects it must be understood that prevention is better than cure. Akathisia, parkinsonism and acute dystonia are less likely to occur if antipsychotic dosages are kept low and high-potency first generation drugs are avoided. If these syndromes occur, one should also consider reducing the dose of the antipsychotic or switching to a drug with less EPS risk.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening, idiosyncratic reaction to antipsychotic medications usually characterized by fever, altered mental status, muscle rigidity, and autonomic dysfunction. A meta-analysis that analyzed the epidemiological data available for NMS in the literature yielded an overall estimate of 0.991 cases per thousand people.[27] Most neuroleptic agents including newer atypical antipsychotics, as well as a variety of other medications that affect central dopaminergic neurotransmission can cause NMS. NMS typically develops within hours or days after exposure to a causative drug. Most patients exhibit symptoms within 2 weeks and nearly all within 30 days.[28]

Typical potent neuroleptics such as haloperidol, fluphenazine, chlorpromazine, trifluoperazine, and prochlorperazine have been most frequently associated with NMS and is thought to possess the greatest risk. A significant number of cases have been reported with most atypical neuroleptics though the risk is thought to be low.[28] In patients on parkinsonism medication abrupt cessation or reduction in dose of dopaminergic medications such as levodopa precipitates NMS. Rare associations have been seen with a number of other medications not known to have any central antidopaminergic activity such as lithium, desipramine, trimipramine, dosulepin, and phenelzine.[27]

The pathophysiology of NMS are complex and one of the widely accepted theories are a marked and sudden reduction in central dopaminergic activity resulting from D2 dopamine receptor blockade within the nigrostriatal, hypothalamic, and mesolimbic/cortical pathways.[29] This explains the clinical features of NMS including rigidity, hyperthermia, and altered mental status, respectively. The primary cause of NMS is the blocking of dopamine receptors by the drugs, particularly the D_2 receptors. The syndrome can also be induced by abrupt dopamine withdrawal. Another theory is the sympathoadrenal hyperactivity, resulting from the removal of tonic inhibition within the sympathetic nervous system. The frequent presence of autonomic symptoms in NMS as well as demonstrated changes in the urine and plasma catecholamine levels in patients with NMS shows abnormalities in the sympathetic system.

Release of calcium has been shown to be increased from the sarcoplasmic reticulum of muscle cells with antipsychotic usage, possibly leading to increased muscle contractility and rigidity, breakdown of muscle, and hyperthermia shows an involvement of the peripheral muscular system activity.[30]

After the causative drug has been discontinued general supportive management and non-specific pharmacological treatment including rehydration, cooling and the treatment of any intercurrent infection should be employed. Semi-recumbent positioning must be employed to reduce the risk for aspiration pneumonia. Benzodiazepines have been used in treatment to facilitate muscle relaxation. Labile hypertension is controlled by the use of calcium channel blockers, because as based on the musculoskeletal toxicity hypothesis they could have a beneficial effect at the musculoskeletal fiber. Low molecular weight heparins are administered to prevent the occurrence of pulmonary thromboembolism. Laboratory values such CPK must be routinely monitored to assess for renal failure. Specific treatment involves the use of dantrolene, amantadine or bromocriptine. Studies showed that the fastest resolution of NMS was achieved first by bromocriptine followed by dantrolene.[31] Use of lorazepam and ECT are also being studied successfully for the resolution of NMS.[32]
After an episode of NMS one should not automatically restart antipsychotic treatment, rather the provider must weigh up the potential benefit over risk of the antipsychotic treatment for that individual and either rechallenge or opt for an alternative agent.

Sleep disorders

Sleep disorders are associated with an increased risk for physical and mental illness and may affect impulse control, impair cognition, mood and emotion regulation in the patient. Antidepressants such as SNRIs are associated with frequent complaints of insomnia and daytime somnolence.[33] Older SNRIs such as venlafaxine and duloxetine show higher cases.

Daytime somnolence is seen to be common adverse effect of mirtazapine. 54% of patients treated with mirtazapine in clinical trials reported somnolence as an adverse event.[34] This is because of the unique pharmacologic profile of mirtazapine which produces relatively more sedation at doses less than 30 mg per day. In patients with depression mirtazapine has been shown to significantly increase total sleep time and sleep efficiency and significantly reduce sleep onset latency, without significantly altering rapid eye movement in sleep parameters. Administration of bupropion reports of insomnia in patients treated for depression and seasonal affective disorder with rates ranging from 11% to 20%.[35] Somnolence, insomnia, and abnormal dreams were some of the common adverse effects in seen with the newer drug vilazodone.[36] Tertiary amine tricyclic antidepressants such as amitriptyline and trimipramine tend to be more sedating, whereas secondary amine TCAs (desipramine, nortriptyline) tend to be more activating. [37] Patients treated with monoamine oxidase inhibitors (MAOIs) reported frequent complaints of insomnia, especially with tranylcypromine.[38] Daytime somnolence and sedation seem to be a common problem with antipsychotics over insomnia. While the mechanism of action is not clear antipsychotics are thought to exert much of their indicated effects through antagonism of dopamine receptors.[39] Many typical and atypical antipsychotics also have seen to exert effects on various monoamines as well as histamine and muscarinic cholinergic receptors. Stimulants commonly prescribed for the treatment show a complex relationship with sleep. Insomnia is one of the most common adverse effects associated with stimulant medications. Effects of methylphenidate on sleep depends on how long the child has been on the medication. [40]

Conclusion

We would recommend the usage of psychotropic agents as per guidelines but, also tailored for each patient based on their history of drug use and presence of other neurological or psychiatric disorders. Since the neuropsychiatric adverse effects are vague and the subjective complaints are confusing it is often hard to perceive, and their occurrence is regularly disparaged. It turns out to be significantly difficult for patients and affects their quality of life. Lasting side effects may lead to further complications. Regular monitoring of the patient, rechallenging techniques and switching should be employed when high risk drugs are being used. Awareness about psychotropic drugs associated with neuropsychiatric side effects may improve overall healthcare. Diligent vigilance and the availability of more comparative data is required to find out potential ADRs to tailor optimum therapy for the patients. Pharmacists should therefore participate in clinical rounds and document procedures to ensure safe use of these drugs to therefore help tailor the ideal pharmacotherapy for the patients.

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