Chapter 24

Psychopharmacology: The Use Of Medication To Treat Challenging Behaviour In Children And Adolescents

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The importance of psychopharmacology to treat severe psychiatric disorder is good evidence of the importance of neuropsychiatric or brain processes. This chapter examines the six major neurotransmitters [glutamate, Gamma-Amino Butyric Acid (GABA), acetylcholine, serotonin, noradrenaline and dopamine] in the human brain and available drugs which target them. Newer atypical neuroleptic agents, attention-deficit hyperactivity disorder (ADHD) medications and an approach to managing self-injurious behaviour are covered in greater detail. When prescribing medication to modulate behaviour in children and adolescents, the clinician must be cognisant of the neurotransmitter targeted. The complex interplay between drug, neuronal circuitry and internal environment must be evaluated and the child monitored for any adverse effects. Guidelines for psychopharmacotherapeutic drug prescribing are provided.

Introduction

The advent of multiple novel psychotropic medications has meant that the contemporary clinician must adopt the role of a pharmacologist when prescribing. All medications have differing target receptors and many have been poorly studied in children. This chapter aims to outline the main neurotransmitters of interest in mental health and their neuronal mechanisms, their pathways, the various mechanisms of action drug classes, expected adverse effects and guide to the selection of medication for specific challenging behaviours.

It must be cautioned that this is a potted précis and it is provided to illustrate some of the mechanisms of an individual's internal environment. Remember for every neurotransmitter action or agonist effect, there are feedback systems that also activate the opposite counterbalancing effect or antagonism. In mental health, clinicians are

primarily concerned with altering the environment to improve mental health. In more severe cases of behaviour disturbance, clinicians necessarily have to consider the internal environment, as a means of environmental manipulation. Genetic studies, for example, comparing monozygotic (identical) twins with dizygotic (fraternal) twins, and twins reared together versus twins reared in different families, enable us to determine to what extent components of patterns of behaviour are genetic or environmental (Thapar & Rutter, 2008). For example, ADHD, Autism and Anorexia Nervosa are all highly genetic, with genetic factors accounting for 80% or more of the variance of behaviour. This genetic factor is often described as the internal environment, because it is not so much the gene that matters but how the gene influences brain development, neuronal connectedness, and molecular and neurotransmitter capacity. The genetic or internal environmental component of depression and panic disorder is moderate, and the influence of conduct disorder in the absence of ADHD is less. However if 85% of the environmental effect on a type of severe behaviour pattern is from the internal or neurochemical and other molecular biology components of the brain environment, that leaves only 15% for external environmental influences, such as relationships, communication, stimulation and thoughts. It may be that clinicians only understand 15% of the internal environment, but this knowledge has had a huge influence on reducing suffering and disability in mental illness. This chapter is an introduction to some landmarks and topography of what is known of the internal world.

After detailing the major and most clinically significant neurotransmitters in the brain governing behaviour, this chapter then examines two specific conditions, Attention-Deficit Hyperactivity Disorder (ADHD) and self-injurious behaviour in closer

detail. A summary of new atypical neuroleptics agents and their rationale for use is also provided.

Neuronal Activity Of The Brain

Modulation of neuronal activity via neurotransmitters is a fundamental mechanism of brain function. The elegant model is the neuronal synapse (see Figure 24.1). Psychopharmacology works to facilitate or inhibit neurotransmitter release, stimulate or hinder synaptic uptake of the neurotransmitter and/or modulate the number of post-synaptic receptors (Stahl, 2008). Drugs achieve this usually after binding to specific receptors on the neurone which then cause changes in the electrical activity or conversely increase the resting membrane potential of the cell to 'inhibit' it. The expression of specific genes (gene regulation) and production of proteins (e.g., post-synaptic receptors) may also occur.

[Insert Figure 24.1 here]

Disorders of neuronal gene expression and cell function (the oft-quoted 'chemical imbalance') are believed to underlie the deficit in neurodevelopmental and psychoaffective disorders (such as depression) (Siever & Davis, 1985; Stahl, 2008). The use of psychotropic drugs aims to correct this imbalance. Often the delay in the effect of psychotropic drugs is due to a secondary effect such as a change in the number of post synaptic receptors, as a result of the increase in neurotransmitter release caused by the medication. It may be this secondary effect, such as is found in the therapeutic effect of

antidepressants, which results in psychotropic drugs not having habit forming or addictive consequences.

Modern day understanding of behaviour involves the concept of 'neuronal circuitry', that is, where neurones are arranged in distributed networks of brain regions to govern human behaviour (Mesulam, 1998) (see Figure 24.2). The prefrontal cortex (PFC) is found in the cortical regions of the frontal lobe of the brain which are anterior to the primary and association motor cortices. The PFC is divided into the dorsolateral, orbitofrontal (also called the limbic frontal lobe) and mesial prefrontal areas. It has a role in integrating, linking and regulating emotional output or responses from deeper brain structures. Emotions modulated by the PFC include pleasure, pain, aggression, anger, fear, reward, panic and basic sexual responses. It is the body's 'decision-maker' and is involved in impulse-control. The PFC is postulated to be able to 'recruit' other processes in the brain to facilitate *adaptive reasoning*. By manipulating neurotransmitters found in the PFC the aim is to modify behaviour.

There are four major *anatomical* systems which govern behaviour, each characterised and modulated by a specific neurotransmitter. These are as follows:

1. The *thalamus* processes all incoming somatosensory, auditory, and visual information before it reaches the cortex.
2. The *association cortex* integrates information from the primary cortices, subcortical structures, and brain areas affiliated with memory to create an internal representation of the sensory information.
3. The *medial temporal lobe* (hippocampus, amygdala) integrates multimodal sensory information for storage into and retrieval from memory, as well as attaches emotional significance (pleasant or unpleasant, 'fight or flight' response).

4. The *basal ganglia* predominantly integrate motor cortical input.

[Insert Figure 24.2 here]

Although there are many more neurotransmitter systems in the brain, clinical psychopharmacology is primarily concerned with the glutaminergic, GABAminergic, cholinergic, serotonergic, noradrenergic and dopaminergic systems. The glutaminergic and Gamma-Amino Butyric Acid (GABA) or 'GABAminergic' systems have the most prevalent and widely distributed neurones in the brain and thus modulation of these affects many neural systems within the brain. The other four neurotransmitter systems originate from densely packed neuronal projections of the forebrain and brainstem to selected neural systems, their modulation leading to more circumscribed effects.

In simplified terms the main neuroanatomical origins of these neurotransmitters to the forebrain and cerebrum are:

- Cholinergic neurones: a network that mainly originate in the basal forebrain and brainstem and connects to the hippocampus.
- Dopaminergic neurones: originate in the substantia nigra and ventral tegmental area
- Noradrenergic neurones: originate in the locus coeruleus,
- Serotonergic neurones: originate in the raphe nuclei

Glutaminergic Neurotransmission

Glutamate is the most abundant neurotransmitter in the Central Nervous System (CNS). It also functions as an intermediate in neurotransmitter metabolism, being a precursor for Gamma-Amino Butyric Acid (GABA). Approximately 30% of the total glutamate in

the brain acts as the major excitatory neurotransmitter. Glutamate facilitates learning and memory function. The widespread action of glutamate in the brain is felt not to have an explicit role in specific psychiatric disorders.

Glutaminergic neurones are widely distributed throughout the brain. Prominent glutaminergic pathways include cortico-cortical projections, connections between the thalamus and cortex, projections from cortex to striatum ('extrapyramidal pathway') and to brainstem or spinal cord ('pyramidal pathway'). The hippocampus and cerebellum also contain many glutaminergic neurones. Glutamate acts on many receptors, most notably the N-methyl-D-aspartate (NMDA) receptor which the illicit drug *ecstasy* targets. Glutaminergic neurons and NMDA receptors in the hippocampus are important in the creation of long-term memory (Wilson & Tonegawa, 1997). However, continuous overstimulation (excitotoxicity) of glutamate neurones induces neuronal degeneration and cell death. This may occur in the context of increased levels of glutamate or normal levels and a sensitised neurone. Excess stimulation of glutaminergic receptors, as in seizures or stroke, or the pathological changes in Alzheimers disease (e.g., ischaemia, beta-amyloid deposits, etc) can lead to unregulated calcium ion (Ca2+) influx and neuronal damage (Coyle & Puttfarcken, 1993; Dingledine, McBain, & McNamara, 1990; Loscher, 1998). *Memantine,* an NMDA receptor antagonist, has found a role in treating Alzheimer's disease dementia.

Diminished glutaminergic function is believed to be involved in the formation of psychotic symptoms. Potent NMDA receptor antagonists, phencyclidine (found in the illicit drug *angel dust*) and the anaesthetic ketamine, can induce psychotic symptoms. Additionally glycine, an inhibitory amino acid, can decrease psychotic or negative symptoms in schizophrenia, although it is reported not to be therapeutically useful

(Farber, Newcomer, & Olney, 1999). *Acamprosate*, used to treat alcohol addiction, is a derivative of the amino acid taurine and like alcohol both reduces excitatory glutaminergic neurotransmission and enhances inhibitory GABAminergic neurotransmission.

GABAminergic Neurotransmission

Gamma-Amino Butyric Acid (GABA) is the major inhibitory neurotransmitter in the CNS. Cortical and thalamic GABAminergic neurones are crucial for the inhibition of excitatory (glutaminergic) neurones. Aside from local circuit neurones ('interneurones') in the cortex, striatum (part of the basal ganglia), cerebellum, and spinal cord; GABAminergic neurones radiate from the caudate/putamen, via the globus pallidus, to the thalamus and substantia nigra (and back to the thalamus and superior colliculus), and from the septum pallucidum to hippocampus.

GABA acts on two receptors, $GABA_A$ and $GABA_B$. Benzodiazepines, such as *diazepam*, bind to the α-subunit of the $GABA_A$ receptor, opening a chloride channel to decrease the excitability of the cell. Barbiturates and ethanol (alcohol) bind near the chloride channel (independent to the presence of GABA) to increase channel opening time and cause cell inhibition (which manifests as drowsiness and sedation). Thus benzodiazepines and barbiturates are efficacious in the treatment and prevention of seizures. The similar mechanism on $GABA_A$ receptors of benzodiazepines and ethanol is the basis for utilising benzodiazepines in alcohol detoxification (Grobin, Matthews, Devaud, & Morrow, 1998). Modulation of $GABA_A$ receptors is beneficial in the treatment of anxiety disorders, insomnia and agitation, most likely due to a generalised inhibition of neuronal activity (Olsen & Tobin, 1990; Stahl, 2008). Baclofen is an

agonist at presynaptic (reducing neurotransmitter release) and postsynaptic (causing decreased excitability) $GABA_B$ receptors (Dutar & Nicoll, 1988; Stahl, 2008). It is primarily used as a muscle relaxant in cerebral palsy to treat spasticity.

Cholinergic Neurotransmission

Cholinergic neurones project from the basal forebrain to the entire cortex, hippocampus and amygdala and from the brainstem to thalamus. Cholinergic interneurones in the striatum modulate the activity of striatal GABAminergic neurones. In the peripheral nervous system (PNS), Acetylcholine (ACh) is the neurotransmitter in the autonomic ganglia, parasympathetic postganglionic synapse (which modulates heart rate via the vagal nerve), and the neuromuscular endplate. This accounts for anticholinergic drugs' adverse effects and potential toxicities. ACh acts at *muscarinic* and *nicotinic* (mostly PNS) receptors. Presynaptic cholinergic receptors can modulate the release of several neurotransmitters (Wonnacott, 1997). ACh is removed from the synapse through hydrolysis into acetyl-CoA and choline by the enzyme *acetylcholinesteras*e (AChE). Removing ACh from the synapse can be blocked irreversibly by organophosphosphate compounds (such as toxic pesticides) and botulinum toxin (Botox), and in a reversible fashion by AChE -blocking drugs such as physostigmine, used in myasthenia gravis.

Cholinergic neurotransmission modulates attention, novelty seeking and memory via forebrain projections to the cortex and limbic structures. Alzheimer's disease (AD) and anticholinergic delirium are examples of an ACh-deficient state. Enhancing synaptic levels of ACh via blocking AChE function strengthens cognitive function in AD and has yielded a whole new class of drugs (*anticholinesterase inhibitors*) used to treat dementia (e.g., rivastigmine) (Geula, 1998; Giacobini, 1998).

Brainstem cholinergic neurones are essential for the regulation of sleep-wake cycles via projections to the thalamus. Cholinergic interneurones modulate striatal neurones by opposing the effects of dopamine. Parkinson's disease is a disorder of dopamine deficiency with effects modulated by acetylcholine (ACh). Increased cholinergic tone in Parkinson's disease and decreased cholinergic tone in patients treated with neuroleptics highlight an imbalance of these two systems in the striatum.

Serotonergic Neurotransmission

Serotonergic (or 5-hydroxytryptamine, 5-HT) neurones project from the midline brainstem (raphe nuclei) to the thalamus, hypothalamus, amygdala, striatum, and cortex. Other fibres project to neurones within the brainstem, to the cerebellum, and spinal cord. Peripherally, serotonin acts as a vasoconstrictor (as in migraines) and a vasoactive procoagulant. Blockade of 5-HT receptors in the area postrema by drugs such as *ondansetron* decreases nausea and vomiting. These widespread serotonergic projections and the heterogeneity of serotonergic receptors modulate many brain functions including mood (anxiety, depression), behaviour (obsessive-compulsive actions, motivation), and the concept of self (schizophrenia). Hallucinogens such as lysergic acid diethylamide (LSD) modulate serotonergic neurones via serotonergic autoreceptors. The concept of 'theory of mind', often deficient in individuals with Autistic Spectrum Disorders, has been postulated to be due to loss of the integrity of serotonergic and dopaminergic neurotransmitter pathways (Abu-Akel, 2003).

Serotonin deficiency within the brain is known to predispose to depression, anxiety, suicidality, violent behaviour, and migraine headaches. Links have also been made between low serotonin levels and pre-menstrual stress, obesity, compulsive

gambling, insomnia, Seasonal Affective Disorder (SAD), and alcoholism. Long term psychosocial stress causes atrophy in the size and number of hippocampal astrocytes (neurones) seen in a variety of psychiatric and neurological disorders, including recurrent depression, schizophrenia, bipolar disorder, post-traumatic stress disorder, epilepsy, head injury, and Alzheimer's disease (Dhikav & Anand, 2007). This may be an underlying aetiology for the increased mortality seen in such conditions as depression following cardiac infarction. Studies have shown that lithium and selective serotonin reuptake inhibitors (SSRIs), such as *fluoxetine*, are neuroprotective in preventing hippocampal atrophy and cell death (apoptosis) (Boldizsar, Simon, Schmelting, Heimke, & Fuchs, 2006).

Repetitive behaviours that are often found in individuals with autism (such as head banging, hand-flapping and body rocking) have been likened to the stereotypies of Obsessive Compulsive Disorder (OCD), and the notion that autism is a serotonin-deficient state (Whitaker-Azmita, 2001; Herault et al., 1996). Serotonin reuptake inhibitors, including clomipramine and SSRIs, may be useful for reducing stereotypical repetitive behaviour in autism and other pervasive developmental disorders. They may also reduce aggression and improve aspects of social relatedness, particularly reduced echolalia and repetitive questioning. It should be noted that haloperidol (blocking dopaminergic neurotransmission) has also been found to reduce stereotypical behaviour and activation, though it is less tolerated due to sedative side-effects (Malone, Cater, Sheikh, Choudry, & Delaney, 2001).

Noradrenergic Neurotransmission

Approximately half of all noradrenergic neurones are located in the locus coeruleus, innervating the cortex, hippocampus, thalamus, cerebellum, and spinal cord. The remainder are distributed in the tegmentum innervating the hypothalamus, basal forebrain, and spinal cord. In the PNS, noradrenaline is the neurotransmitter of the sympathetic postganglionic synapse and contributes to hypertension and the adrenal glands' 'fight-or-flight' crisis response of affective driven aggression or panic. β-adrenergic blocking agents ('β -blockers'), such as *propranolol*, are used to antagonise adrenergic and noradrenergic effects both peripherally and centrally.

Noradrenergic projections in the thalamus, limbic structures and cortex modulate sleep cycles, appetite, mood and cognition. These functions are targeted by antidepressant drugs. The great number of noradrenergic neurones (receiving afferent stimuli from both internal and external environments) in the locus coeruleus, is believed to be crucial to the 'fine-tuning' of *attention* of the cerebral cortex, such that perturbations of this system may result in feelings of anxiety (Svensson, 1987). Locus coeruleus neurones express a variety of autoreceptors. The firing of these may be reduced by *clonidine* (Buccafusco, 1992) which has been used in ADHD and as an anxiolytic and to control explosive outbursts. Parents should be advised to avoid abrupt discontinuation of clonidine to prevent rebound increases in blood pressure, tics and anxiety (Leckman et al., 1986). Opioids, such as *morphine*, decrease locus coeruleus firing and opioid withdrawal leads to increased firing. This is the rationale for clonidine use in the treatment of opioid withdrawal syndrome.

Reboxetine is a selective noradrenaline reuptake inhibitor, effective as an antidepressant. It may also have a role in Attention-Deficit Hyperactivity Disorder (ADHD). *Mirtazipine*, another atypical antidepressant, is less selective. It acts primarily

through α_2-noradrenaline presynaptic and 5-$HT_{2A/3}$ postsynaptic antagonism respectively, leading to increases in noradrenaline and 5-HT_{1A} activity. The antidepressant *venlafaxine* is a selective serotonin and noradrenaline reuptake inhibitor (SSNRI). *Atomoxetine* (discussed below) a drug used in ADHD increases both noradrenaline and serotonin synaptic concentrations. The tricyclics antidepressant *amitriptyline* increases synaptic concentrations of noradrenaline and dopamine greater than that of SSRIs and may be useful in treating aggression.

Dopaminergic Neurotransmission

Dopaminergic neurones are significantly found in the substantia nigra (SN), radiating to the caudate and putamen, and ventral tegmental area (VTA). The VTA neurones project to limbic regions (nucleus accumbens, amygdala) or *mesolimbic system,* and cortex (frontal, cingulated, entorhinal) or *mesocortical system*. Dopaminergic neurones also project from the hypothalamus (including the pituitary gland) and are found in the retina and olfactory bulb. Dopaminergic projections from the hypothalamus to the pituitary gland tonically inhibit the production and release of prolactin via D_2-receptors. Blockade of these receptors, such as with neuroleptic drugs, leads to *hyperprolactinaemia* and *galactorrhoea*, a common and unwanted adverse effect. SN dopaminergic neurones modulate the function of striatal GABAminergic neurones. Parkinson's disease and extrapyramidal side-effects (discussed further below) following treatment with neuroleptics are examples of decreased dopaminergic function.

The mesolimbic system is known to be involved with *reward behaviour* and in the development of *addiction* to drugs such as ethanol, cocaine, nicotine, and opiates (Diana, 1998; Koob, 1998). The mesocortical system's role is to fine tune memory and

cognition (Goldman-Rakic, 1998). Dopamine is an intermediate monoamine in the synthesis of noradrenaline and adrenaline, as well as being a neurotransmitter in its own right. Dopamine is synthesised by the enzyme *L-aromatic amino acid decarboxylase* from DOPA. Dopamine levels can be elevated if extra DOPA is supplied to the brain, such as L-DOPA administration in Parkinson's disease. Dopamine is released into the synapse from vesicles, a process facilitated by *amphetamines*, such as *dexamphetamine* or *methylphenidate* (Ritalin). Amphetamines may precipitate psychosis. *Tetrabenazine* is a non-neuroleptic that depletes presynaptic dopamine and has weak post-synaptic dopamine-blocking properties. It has found a role in reducing motor tics in Tourette's syndrome.

Pergolide is a mixed D_2/D_1 agonist developed for the treatment of Parkinson's disease. The theory behind using a dopamine *agonist* to treat tics is in its postulated function in 'balancing out' dopamine neurotransmission. In conditions such as Tourette's syndrome with heightened dopaminergic tone, pergolide acts as a dopamine antagonist. By contrast, in Parkinson's disease with decreased dopaminergic activity, pergolide acts as a dopamine agonist. Pergolide's formal role in the treatment of Tourette's syndrome is yet to be defined (Lipinski, Sallee, Jackson, & Sethuraman, 1997). *Amantadine*, an antiviral agent used in Parkinson's disease, potentiates dopaminergic neurotransmission by blocking dopamine reuptake into presynaptic neurones and stimulating CNS dopamine release.

Attention-Deficit Hyperactivity Disorder (ADHD)

The pattern of neuropsychological deficits found in children with ADHD implicates deficits in executive function and working memory (Barkley, 1997). This pattern is

similar to that found amongst adults with frontal lobe damage, suggesting dysfunction of the frontal lobe or regions projecting to it. It has been postulated that ADHD consists of deficits in noradrenergic inhibitory influences of frontal cortical activity, driven by dopamine agonists acting on lower striatal structures (Zametkin & Rapoport, 1987). In several studies, stimulants appear to 'normalise' ADHD behaviour (Whalen, 1989) in children including increased ability to perceive peer communications, self-perceptions and situational cues. These children show improved modulation of the intensity of behaviour, improved communication and greater responsiveness (Whalen, Henker, & Granger, 1990). Additionally, stimulant-associated improvements in social interactions positively influence the social behaviour of others in the child's environment (Whalen & Henker, 1992; Cunningham, Siegel, &Offord, 1991). Parents, teachers, siblings and peers are more positive and less critical of the child with ADHD who is receiving stimulant medication. Studies have also indicated that both behaviour and cognitive performance improve with stimulant treatment in a dose-dependent fashion (Douglas, Barr, O'Neill, & Britton, 1988; Rapport, Quinn, & DuPaul, Quinn, & Kelly, 1989). Doses that improve behaviour rarely constrict attention or lead to 'over-focussing' (Douglas, Barr, Desiletes, & Sherman, 1995; Solanto & Wender, 1989). When negative social behaviour and deficits are associated with ADHD-type symptoms, pharmacotherapy is a useful treatment modality. However improvement of the internal environment by Ritalin should be used to potentiate the external environment, in terms of enhancing developmental promotion in the family, school and community.

Atomoxetine blocks presynaptic reuptake transporters in the pre-frontal cortex creating an equivalent increase in noradrenaline and serotonin there. It does not increase dopamine within the nucleus accumbens, so lacks euphoric effects or reinforcing

properties, so has no potential for drug abuse. It also does not increase dopamine within the striatum, so is not associated with motor or vocal tics that stimulant treatment of ADHD may cause. Atomoxetine acts specifically on noradrenergic neurotransmission so has no effect on cardiac conduction (and potential arrhythmic side-effects) in comparison to tricyclic antidepressants.

Monoamine Oxidase Inhibitors (MAOI)

MAOIs inhibit the intracellular catabolic enzyme *monoamine oxidase*. Both types, MAO-A and MAO-B metabolise tyramine and dopamine. Additionally, MAO-A preferentially metabolises noradrenaline, adrenaline, and serotonin. Irreversible MAOIs (e.g., phenelzine, tranylcypromine) traditionally used to treat depression in adults, have the potential for 'hypertensive crisis' should the patient ingest tyramine-rich foods (such as cheddar/aged cheeses, broad or fava beans, fish especially pickled e.g., herring, red/Chianti wine, beer and some liqueurs, meat e.g., pepperoni sausage, yeast products and banana peel) or concurrently take sympathomimetics or amphetamines. A serotonergic syndrome may develop when MAOIs are combined with SSRIs. These dietetic restrictions and potential drug-to-drug interaction limit the use of irreversible MAOIs in children, however preliminary studies suggest that MAOIs are effective in ADHD (Zametkin, Rapoport, Murphy, Linnoila, & Ismond, 1985). Notably, the non-selective reversible MAOI *moclobemide* does not possess this risk and provides for greater safety when used in children. Its role in the treatment of ADHD is yet to be elucidated.

Buspirone

Buspirone is a non-benzodiazepine anxiolytic with a high affinity for serotonin 5-HT_{1A} receptors, as well as having a modest effect on dopaminergic neurotransmission and α-adrenergic activity. Its anxiolytic effect is believed to result from inhibiting the spontaneous firing of serotonergic neurones in the dorsal raphe nucleus of the hypothalamus by binding to presynaptic 5-HT_{1A} receptors. It reportedly improves disruptive behaviour and psychosocial function, with only mild side effects (e.g., dizziness, nausea, agitation) in children with ADHD (Malhotra & Santosh, 1998). In comparison to benzodiazepines, buspirone has a lower incidence of side-effects, no risk of dependence and no withdrawal syndrome.

Melatonin

Melatonin is the neurotransmitter secreted by the pineal gland. It acts on specific melatonin receptors in the suprachiasmatic nucleus of the hypothalamus to affect sleep onset and regulate circadian rhythm. It may be of benefit in childhood sleep disorders or altered sleep/wake cycles, albeit these may be inherently altered in the child with cortical dysplasia or neurodevelopmental dysfunction. Individuals with Smith-Magenis Syndrome have an inverted circadian sleep/wake cycle with more melatonin produced in the early hours of the day and less at night. Beta-blockers administered in the morning halt the body's production of melatonin whilst melatonin medication is supplemented at night, thus correcting the normal physiological cycle (Cardinali & Pandi-Perumal, 2005; Elsea & Girirajan, 2008; De Leersnyder, Claustrat, Munnich, &Verloes, 2006; De Leersnyder et al., 2001).

Atypical Neuroleptics

Atypical neuroleptic drugs possess potent D_2- and 5-HT_2-blocking properties. This latter activity is believed to account for their ability to improve the negative symptoms of schizophrenia and be protective against extrapyramidal side-effects (such as loss of fluidity of movement), flattening of emotional expression and fine tremor (drug-induced parkinsonism), increased muscle tone and muscular spasms (dystonia), as well as restlessness of limbs (akathisia). The onset of tardive dyskinesia, repetitive involuntary purposeless movements, is also possibly reduced. These putative 'safety' features of atypical neuroleptics make them attractive alternative to the traditional agents, especially if the child with ADHD is to be medicated over several years.

Clozapine

Clozapine, the original atypical neuroleptic, is a potent 5-HT_2 blocker with lesser D_2-antagonism. It has not been associated with significant extrapyramidal symptoms or tardive dyskinesia. Clozapine appears effective in reducing aggressive behaviour (Glazer &Dickson, 1998) and improving quality of life for those with chronic schizophrenia which is resistant to other antipsychotics. Clozapine's major drawback is its 1% risk of potentially fatal agranulocytosis.

Olanzapine

Olanzapine acts similarly to clozapine, however with greater D_2-blockade and much lower risk of agranulocytosis. Like clozapine, it also acts at 5-HT_{2A}, 5-HT_{2C}, D_1, D_2, D_4, muscarinic M_1, α_1-adrenergic and H_1-receptors. Olanzapine's most significant side-effects are sedation and weight gain (Pottenza, Holmes, Kanes, & McDougle, 1999). Each antipsychotic acts uniquely on a varied dopamine receptor subtype which is

an explanation why drugs in the same group may have subtle but different clinical outcomes. Such differences are difficult to predict in any individual case.

Risperidone

By improving the negative signs and symptoms of schizophrenia, risperidone has been trialled in adolescents with autism to treat similar 'withdrawn' behaviour with varying degrees of success. Improvements in aggression, self-injury, explosiveness, overactivity, and poor sleep have been observed with risperidone (Horrigan & Barnhill, 1997). In a head-to-head study with haloperidol, risperidone has been shown to be superior in improving hostility independent from reducing psychosis (Czobor, Volavka, & Meibach, 1995). The most common side-effect with risperidone use is weight gain (proposed to be via H_1- and 5-HT_{2C}-receptor blockade). *Quetiapine* has been reported to be less efficacious and less tolerable than risperidone in pervasive developmental disorders.

Ziprasidone

Although similar to risperidone and olanzapine in blocking D_2- and 5-HT_2-receptors, ziprasidone has additional 5-HT_{1A}- agonist properties and modest noradrenaline and serotonin reuptake blocking action. These may contribute to anxiolytic and antidepressant effects (Chappell, Scahill, & Leckman, 1997).

Aripiprazole

Aripiprazole is a partial dopamine D_2-receptor and 5-HT_{1A} agonist in addition to being a 5-HT_{2A} antagonist (Burris et al., 2002). Significant improvements have been noted

with its use in reducing aggression, self-injury and irritability (Stigler, Posey, & McDougle, 2004). It generally causes less weight gain than olanzapine and risperidone. Aripiprazole causes minimal cardiovascular side-effects.

Mood Stabilisers

Lithium and anticonvulsant drugs have not been found to be effective in treating ADHD but have been found helpful in treating aggression in individuals with developmental disabilities. They also have been used in the management of intermittent explosive disorder (Trimble, 1990). *Carbamazepine* has proved effective in treating lithium-resistant mania.

Selection of an anticonvulsant to treat disruptive behaviour must involve consideration of each drug's potential toxicity and patient tolerability (e.g., valproate-induced hirsutism in adolescent girls). Newer antiepileptic agents (e.g., lamotrigine) may be candidates for novel mood stabilising agents as long as their significant potential toxicities (such as Steven Johnson syndrome, a severe allergic effect) are considered (Folgelson & Sternbach, 1997; Kotler & Matar, 1998; Sporn & Sachs, 1997; Calabrese, Fatemi, & Woyshville, 1996). *Topiramate* is being investigated as a treatment for eating disorders and alcoholism.

Self-Injurious Behaviour

Individuals with intellectual disabilities are more likely to develop psychiatric disorders than the general population (Hardan & Sahl, 1997). Maladaptive and disruptive behaviours such as aggression, self-injury, and stereotypical mannerisms are common.

The presence of any of these symptoms compromises an already limited capacity for adaptive functioning and in some cases this will improve with pharmacological therapy.

The appearance of *self-injurious behaviour* in an individual with severe impairment is non-specific and may be the result of acute medical illness or related to mood, psychotic, anxiety or impulse control disorders. An attempt to identify the antecedents of the behaviour should be made. Common causes may include dysphoria from loneliness, depression and physical pain or another problem with sensory experience or associated arousal modulation. The behaviour should be characterised in terms of precipitating factors, frequency, duration and severity. If the behaviour is of recent and acute onset, the search for any underlying medical pathology is essential. If it is associated with a change in appetite or activity, an underlying mood disorder may be the cause. Avoidant or highly situational behaviours may indicate anxiety, while poor self-restraint proposes an impulse control disorder.

The consequences of the self-injurious behaviour should be identified. Carers may inadvertently reinforce the behaviour by providing attention, undue support and permitting misbehaviour. An objective functional analysis of the behaviour by the clinician may identify more suitable caregiver interventions that do not reinforce the behaviour and also provide appropriate coping mechanisms to the carer. Atypical antipsychotics and SSRIs are the mainstay of treatment for self-injurious behaviour.

Dopamine D1-receptor sensitivity appears to provoke self-injurious behaviour in both animal and human models (Aman, 1993). Congenital dopamine deficiency of Lesch-Nyhan syndrome is thought to underlie the associated self-injurious behaviour. *Propranolol*, a β-adrenergic blocking agent, has been reported to be effective in treating refractory aggression in brain-damaged patients (Kuperman & Stewart, 1987; Grizenko

& Vida, 1988). Interest in the role played by endogenous opiates (endorphins) in the pathogenesis of self-injury has led to the use of opioid-receptor antagonists, such as *naltrexone* and *naloxone* to treat this condition. Studies to date have offered inconclusive results (Barrett, Feinstein, & Hole, 1989; Sandman, Barron, & Coleman, 1990). Clinical algorithms for a multitude of psychoaffective disorders have been proposed, including maladaptive aggression (see Figure 24.3).

[Insert Figure 24.3 here]

The notion of a 'behavioural phenotype' (i.e., the attribution of a specific set of behavioural or psychiatric expressions to an underlying genotype) is popular. This is due in part to advances in molecular genetics and neuroimaging. Nevertheless, the clinician should be familiar with specific syndromic diagnostic possibilities, such as Fragile X, Williams, Prader-Willi, Smith-Magenis and Down syndromes.

Violent behaviour may also be linked to genetic conditions or genetically-determined enzymatic activity. An association between increased violent behaviour and reduced activity of the catabolic *catechol-O-methyltransferase* (COMT) enzyme, leading to higher concentrations of synaptic L-DOPA, has been found (Lachman, Nolan, Mohr, Saito, & Volavka, 1998). The use of pharmacological COMT-inhibitors, *tolcapone* and *entacapone* (as in Parkinson's disease), has similarly been found to induce aggression. Social deprivation in the early years of a child's life has been found to have an interactive gene-environment 'multiplier effect' leader to higher rates of antisocial behaviour (Henry, Caspi, Moffitt, & Silva, 1996). Psychosocial stimulation plays a vital part in neurodevelopment. Prolonged deprivation is associated with a

proportional stunting of brain growth (smaller head circumference), lower IQ, and increased mental health problems, independent of nutrition (Sonuga-Barke et al., 2008).

In general, psychopharmacological treatments for disorders of maladaptive aggression are adjunctive to psychosocial, psycho-educational and community treatment plans. Comorbid paediatric psychotic disorders with aggression as a significant associated symptom should be diagnosed and treated. These include: ADHD, anxiety, depression, adolescent bipolar disorder, Post-traumatic stress disorder (PTSD), and psychosis, which must be assessed in the context of the child's developmental age.

Pharmacogenomics

The response of a drug response within a patient as determined by their genetic expression, e.g., enzyme concentration, is termed *pharmacogenomics*. This may be particularly important in the cytochrome P450 pathways of hepatic metabolism of psychotropic medication. A few centres are already testing a patient's cytochrome P450 genotypic expression with the aim of selecting a personalised therapeutic dose and avoiding potential dose-related side-effects.

Process Of Psychopharmacotherapy

1. Select an appropriate pharmacological agent (and dose *form*). Be alert for drug-drug interactions.
2. Determine an initial target dose, ideally once a day, according to lean body weight or surface area.
3. 'Start Low and Go Slow' - Gradually escalate dose to optimum level.
4. Wait an expected length of time for the therapeutic effect to occur.

5. Assess the response (ideally using an objective rating scale).
6. Be alert for adverse effects.
7. Consider augmentation (adding another agent) or substitution (using a different compound with the same therapeutic indication).
8. Step-down ineffective medication doses and allow an appropriate washout period (4-5 half-lives).
9. If all else fails, review the diagnosis.

Conclusion

Psychopharmacology uses drugs to modulate neurotransmission within anatomical systems to influence behaviour. Our current understanding of these complex networks is rudimentary and fraught with unwanted adverse effects (see Table 24.1). Psychopharmacology attempts to match a targeted behaviour with an appropriate medication in order to modulate that behaviour (see Figure 24.4).

[Insert Table 24.1 here]

[Insert Figure 24.4 here]

The field currently contains a multitude of medications with little accompanying studies to guide their prescription and use in children. Unusual long term safety data is often the last to be collected. Drug development involves extensive research and testing. More recently this includes safety data in children. Drugs generally have good levels of evidence of effectiveness. Changing the internal environment is not without risk and

proper management of side effects is part of best practice. Over time and through progress, designer drugs will be developed to specifically target localised neuronal receptors and behavioural objectives.

Acknowledgments

The author would like to acknowledge Dr David Dossetor for his kind assistance, clinical experience, and opinion in writing this chapter; and Judith Longworth, Pharmacist (Department of Psychological Medicine, CHW) for reviewing this chapter.

Table 24.1

Summary Of Major Neurotransmitters And Their Respective Adverse Effects

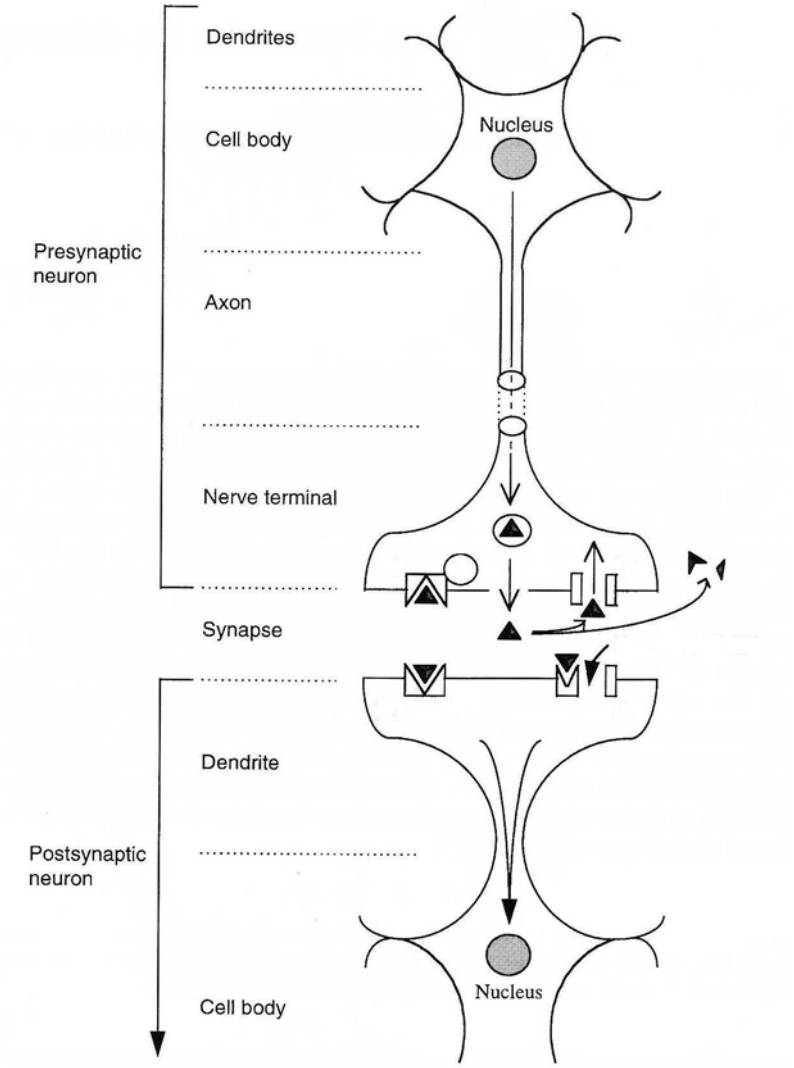
* Anticholinergic side-effects include: dry mouth, urinary hesitancy, blurred vision, constipation, confusion, pupillary dilatation.

Neurotransmitter	**Agonist Example**	**Antagonist Example**	**Adverse Effect**
Glutamate	Monosodium glutamate, ecstasy (not clinically used)	NMDA antagonists, eg memantine	Seizures, encephalopathy, excitation
GABA	Benzodiazepines eg diazepam, barbiturates, gabapentin	Flumazenil (‘benzodiazepine antidote’)	Disinhibition, somnolescence, ataxia, dependence (withdrawal seizures)
Acetylcholine (muscarinic)	AChEs eg rivastigmine, nicotine, bethanecol	Anticholinergic* TCAs eg amitriptyline, benztropine	Salivation, sweating, diarrhoea, urinary incontinence
Serotonin (5-HT)	SSRIs eg fluoxetine	Cyproheptadine	Hypertension, tachycardia, hyperthermia, myoclonus, sweating

Noradrenaline	SNRIs eg reboxetine	β-blockers, eg propranolol	Hypertension, tachycardia, wakefulness
Dopamine	L-DOPA, Dexamphetamine, methylphenidate	Neuroleptics, eg haloperidol	Stereotypies, mania, exacerbation of tics/ movement disorders

Figure 24.1

The Structure Of The Neuronal Synapse

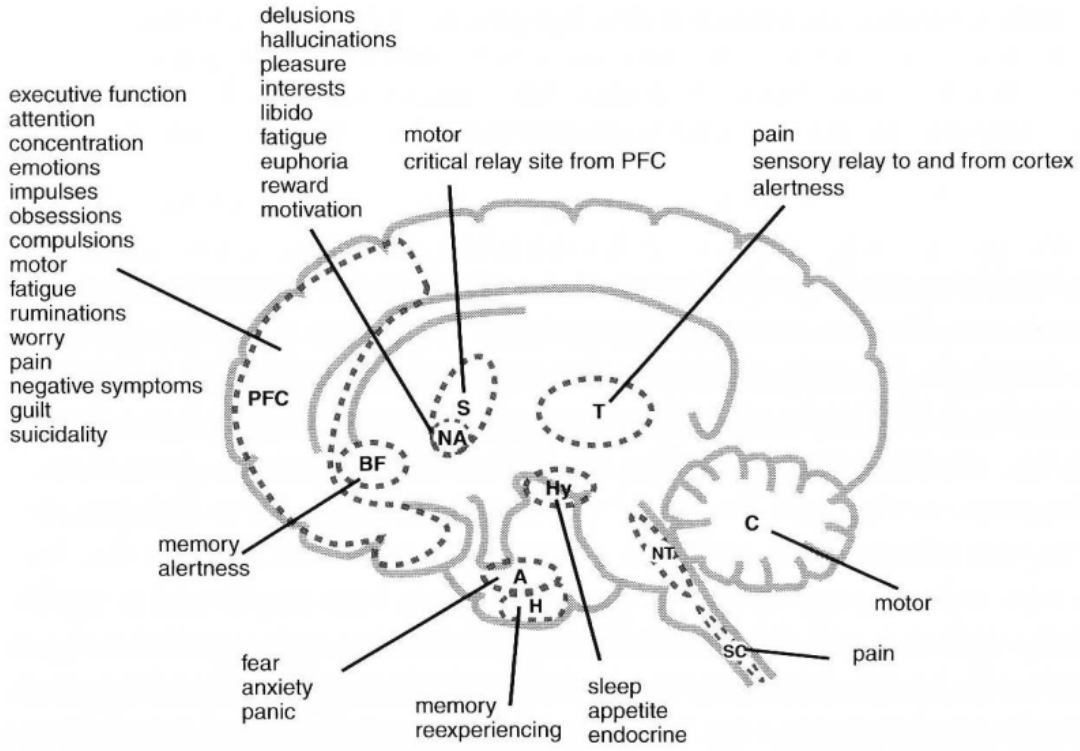


Source: Adapted from Heckers and Konradi (2000, p.2).

Figure 24.2

Behaviours Linked To Specific Brain Regions

PFC, prefrontal and association cortices; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centres (containing substantia nigra, ventral tegmental area, locus coeruleus and raphe nuclei); SC, spinal cord; C, cerebellum. [The basal ganglia containing and spanning the striatum (S) and substantia nigra within the brainstem neurotransmitter centres (NT) is not shown for clarity.]

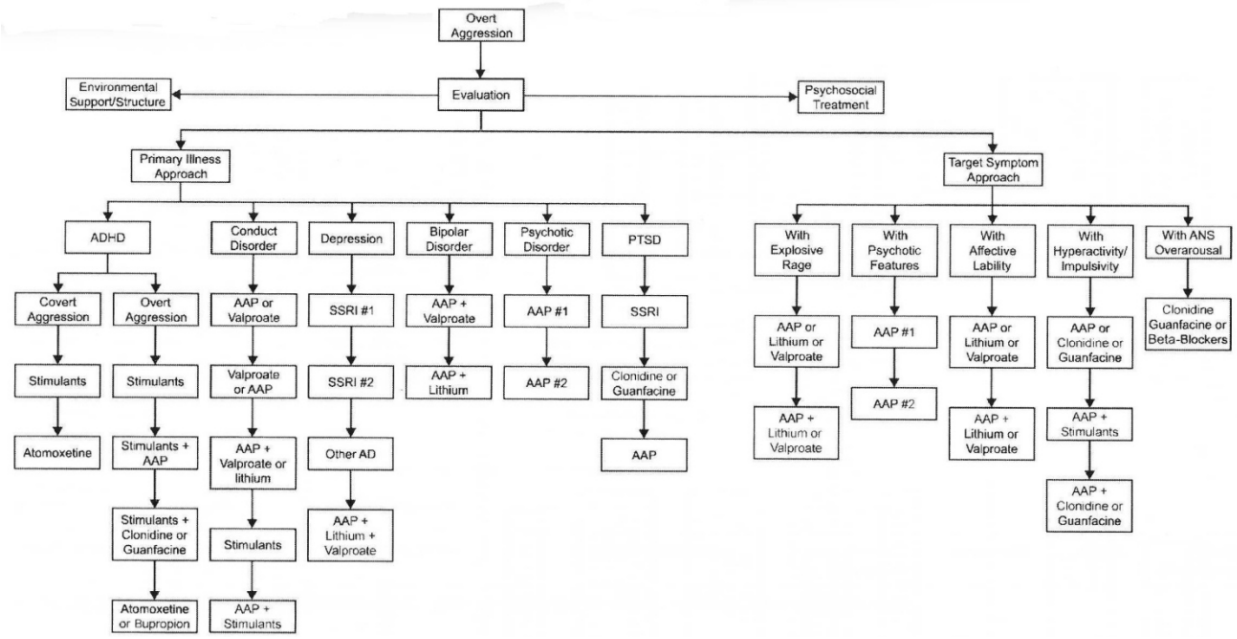


Source: Adapted from Stahl (2008, p. 203).

Figure 24.3

A Clinical Algorithm For The Medical Treatment Of Maladaptive Aggression In Children

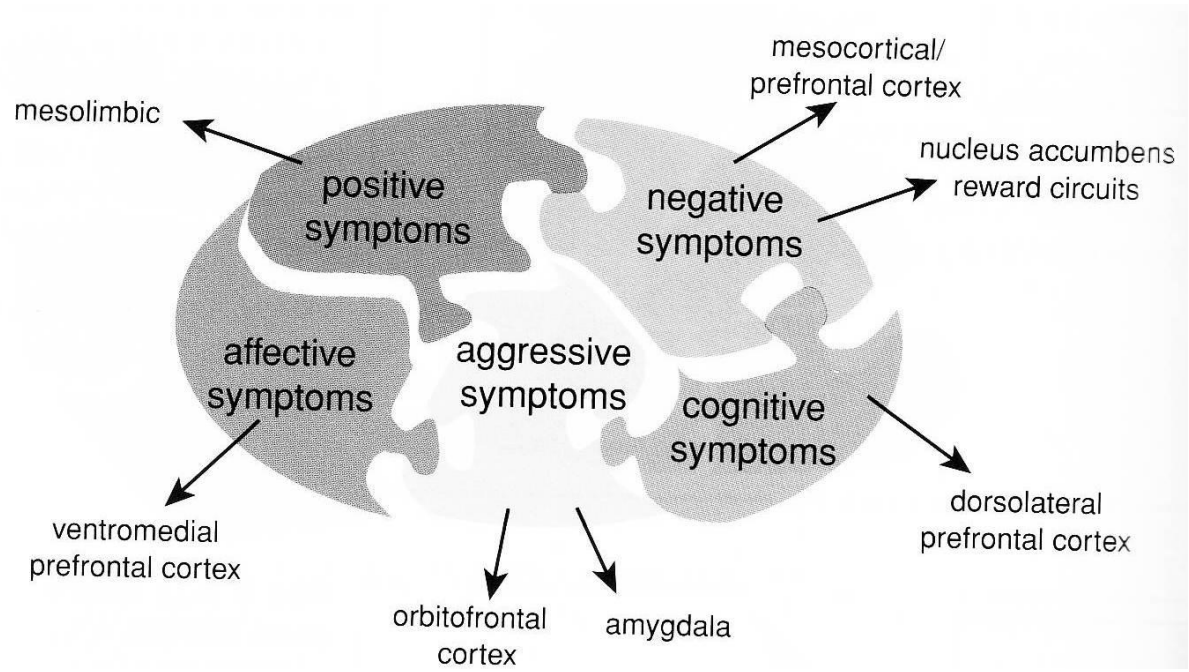
AAP, atypical antipsychotics; SSRI, selective serotonin reuptake inhibitor; AD, antidepressant; PTSD, post-traumatic stress disorder; ANS, autonomic nervous system.



Source: Reproduced from Connor and Meltzer (2006, p. 333) with permission (*pending*).

Figure 24.4

Symptoms (on Schizophrenia) Matched To Malfunctioning Brain Regional Neural Circuits



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