Social engineering and the structure activity relationships (SAR's) of selected mind-altering compounds such as tryptamine and phenylethylamine derivatives

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Abstract

The chemistry of tryptamines and phenylethylamines as both neurotransmitters and as potential agents for social engineering forms a captivating area between chemistry and neuroscience. This article highlights several drugs including phenylethylamine related derivatives such as propranolol, modafinil, methylphenidate, lamotrigine and oxytocin; as well as tryptamine derivatives such as lysergic acid diethylamide and melatonin and investigates the use of these compounds or their derivatives as potential social engineering agents.

Keywords: social engineering, phenylethylamine, tryptamine, structure activity relationships

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1 Introduction

Social engineering is defined as an attempt to control social behaviour. In line with some of the social engineering themes of Aldous Huxley's novel written in 1931 called, "Brave New World", this paper highlights selected structure activity relationships and potential lead compounds which are currently used in modern day medicine and whose chemical derivatives or even themselves *might* be able to address various social issues in the future. Conventional medicines are most often used to treat individuals who have a biological or psychological illness, but could medicines of the future be used to treat countries? If so, who decides what to treat; governments, pharmaceutical companies, doctors etc? Mankind is a product of both nature (genetics) and nurture (upbringing and surroundings) and these parameters are relatively set by the time one is an adult. Could we use mind-altering drugs to benefit or influence mankind's behaviour, his ideas or even his beliefs? This raises further questions such as; can the side effects of medication influence our personal attitudes? Would drugs open the mind to any suggestions or just specific ones? This of course opens a Pandora's Box of ethical and philosophical dilemmas and discussions.

In an overly simplified sentence, some argue that we are all products of the summation of our neurotransmitters (Table 1). Medicines which increase dopamine concentrations in selected areas of the CNS are used to treat Parkinson's disease, such as Levodopa (Madopar®). Conversely, dopamine antagonists include antipsychotics such as Chlorpromazine (Largactil®). Medicines which increase serotonin concentrations in selected areas of the CNS are often used to treat depression, for example selective serotonin re-uptake inhibitors (SSRI's) such as Fluoxetine (Prozac®) (Joint Formulary Committee, 2010). By using mind-altering drugs (such as antidepressants and antipsychotics), it is possible to 'tweak' or manipulate neurotransmitters with very interesting outcomes. Could, for example, drugs of the future be used to change or alter low intelligence quotient (IQ), racial bias, capitalism, extremism, religious perceptions or even help us live longer?

2 Findings

2.1 The possible chemical evolution of mankind?

Carl Sagan and Terrence McKenna have proposed that current day Man would not exist if it was not for mind-altering drugs (Sagan, 1969; McKenna, 1992).

Carl Sagan (an American scientist) proposed that mankind's evolution was jump-started by the cultivation of mind-altering plants such as *Cannabis*. Since agriculture and farming

Table 1: Summary of neurotransmitters and their postsynaptic effects (Mycek *et al.*, 1999)

Neurotransmitter	**Postsynaptic effects**
Acetylcholine	Excitatory - arousal, short-term memory, learning and movement
Norepinephrine (NE) (Biogenic amines)	Excitatory - arousal, wakefulness, mood, cardiovascular regulation
Dopamine (Biogenic amines)	Excitatory - emotion, motor control
Serotonin (Biogenic amines)	Excitatory / Inhibitory - feeding behaviour, body temperature, mood and emotion, sleep / wakefulness
GABA (Amino Acids)	Inhibitory
Glycine (Amino Acids)	Inhibitory
Glutamate (Amino Acids)	Excitatory
Substance P (Neuropeptides)	Excitatory - mediates pain
Met-enkephalin (Neuropeptides)	Generally inhibitory - mediates pain

lead to the development of civilisations, it was suggested that *Cannabis* might have been the first crop to move Mankind from being a hunter-gatherer into his modern day form (Sagan, 1977).

One fairly interesting idea although not fully supported by hard evidence, proposed by Terence McKenna who wrote the book "Food of the Gods" suggests that magic mushrooms, specifically *Stropharia cubensis* were directly responsible for changing apes into humans (McKenna, 1992). *Stropharia cubensis* contains the hallucinogenic psilocybin, which McKenna believes is responsible for the development of language evolution, greater sexual enjoyment and a self-reflective consciousness that distinguishes humans from animals. In addition, he attributes the magic of speech, dance and a sense of religion to the evolutionary effects of psilocybin.

2.2 Tryptamine derivatives

Psilocybin is an indole or tryptamine derivative. Tryptamine is structurally similar or related to the amino acid tryptophan. In the body, a phosphate group is removed from the psilocybin compound and this releases psilocin, an active hallucinogenic compound (Figure 1).

The fact that serotonin is structurally similar to psilocybin or dimethyltryptamine (DMT), for example they are all tryptamine containing substances, is fascinating indeed (Figure 2). This shows that the chemistry of a human neurotransmitter (such as serotonin) is related to that of a plant or fungal alkaloid such as psilocybin. Does this perhaps suggest that there

is a connection between human and fungal or plant chemical evolution?

Distinguished scientist, Francis Crick was awarded a Nobel Prize for his work on DNA. He co-proposed an interesting and fairly radical theory called *panspermia* and suggested that

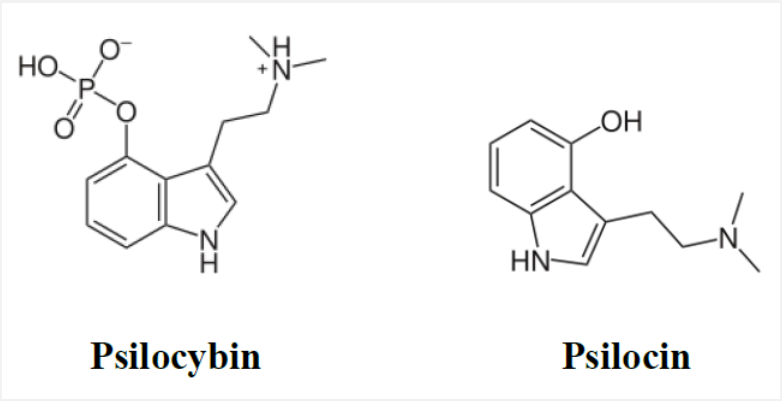

Figure 1: Tryptamine derivatives, psilocybin and psilocin respectively.

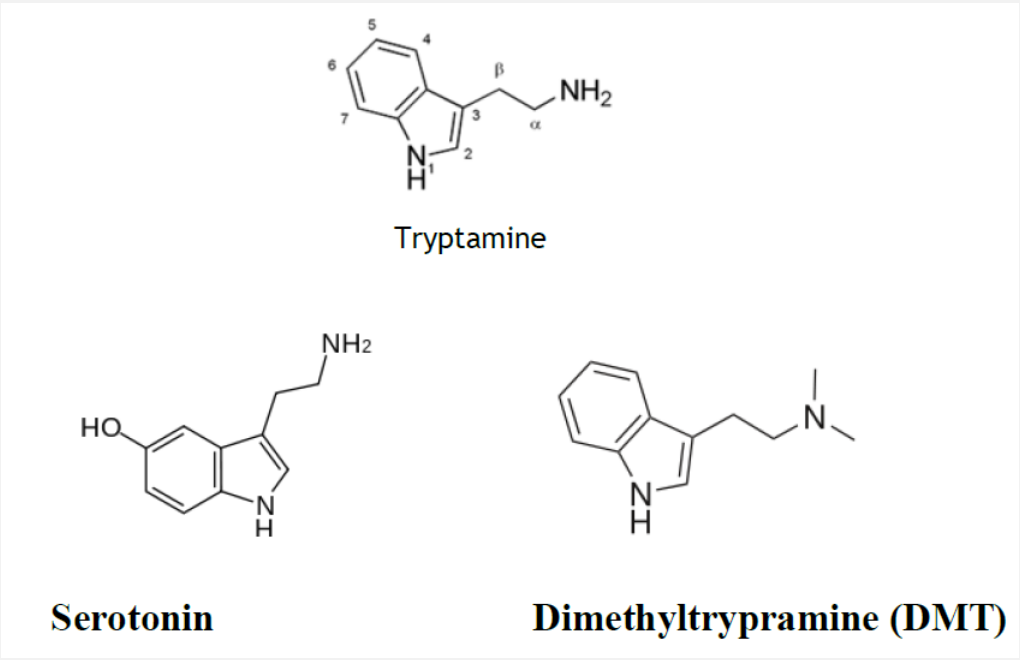

Figure 2: Tryptamine derivatives, serotonin and dimethyltryptamine (DMT) respectively.

all life on earth sprang from spores that arrived here from space. Although a far reach, it is still interesting to note that the spores from *Stropharia cubensis* contain compounds with a chemistry similar to those found in the human brain!

Tryptamine derivatives stimulate the serotonin (5-HT) receptors in the brain and cause euphoric feelings or psychedelic experiences. Psychedelic effects of psilocybin last 2-6 hours and can be either pleasant or unpleasant. The active dose in man is 6-20 mg. Doses of 20-40 mg induce stronger visions (Erowid, 2015).

Tryptamine derivatives such as DMT are very commonly found in nature. Tryptamine derivatives may be found in little marine animals, butterflies, certain species of grass, trees and mushrooms. Most hallucinogenic compounds found in plants will have tryptamine related structures. For example, there are literally 'hundreds' of plants which contain DMT in varying concentrations (Shulgin and Shulgin, 1997). The actions of DMT are characterised by rapid onset of action ($<$ 5 minutes) and short duration of action ($\sim$30 minutes) - it is a relatively weak hallucinogen.

In terms of the structure activity relationships (SAR's) of tryptamines, they need to be sufficiently lipophilic to penetrate the blood brain barrier (BBB). A chemical compound which does not get into the brain is rapidly metabolised by the enzyme monoamine oxidase (MAO). If the N-alkyl or N,N-dialkyl substituents are bulky and lipophilic enough, tryptamines can be orally active (Lemke et al., 2013). Serotonin (5-HT) is not hallucinogenic and does not readily penetrate the BBB when administered systemically.

5-OMe DMT is a constituent of a number of plants used in various concoctions prepared by South American Indians for ceremonial and visionary purposes. 5-OMe DMT is also found in the skin of certain frogs and has given rise to the phenomenon of "toad licking" (Lemke et al., 2013). As a result, some people lick frogs in order to be euphoric.

Tryptamine itself is not psychoactive. However, the introduction of an α-methyl group makes it a psychoactive agent. The methyl group seemingly enhances its lipophilicity and sufficiently protects the compound against metabolism. This introduction of the methyl group also creates a chiral centre of which the S (+) isomers of α-MeT's are more potent than the R (-) isomers. Extending the methyl group to an ethyl group is also renders it a hallucinogenic agent. The α-EtT compound was available in the 1960's as an antidepressant called Monase®(Lemke et al., 2013).

Lysergic acid diethylamide (LSD) also has an indole or tryptamine nucleus (Figure 3). Although LSD is a synthetic product, it is a member of the ergot alkaloid family. Lysergic acid (which is similar to LSD) often appears as a metabolic product of the fungus *Claviceps purpurea* which is found on barley or rye. During medieval times (in Europe) this fungus was responsible for 'St. Anthony's Fire' (Krska and Crews, 2008). By making bread with

rye that was contaminated with this fungus, people would often simply go mad. Instead of receiving medical attention, people were often burnt alive as it was believed that they were possessed by a demon. It is known as 'St. Anthony's Fire' because of the intensive burning sensation due to the vaso-constrictive effects produced by the ergot alkaloids. Some even argue that the hallucinogenic fungus *Claviceps purpurea* containing lysergic acid amides might also have triggered the French Revolution. Because during this time there was a lack of food or bread and contaminated rye might often have been used. Three major effects are produced; perceptual (altered shapes, colours and a heightened sense of hearing); psychic (alterations in mood, depersonalisation and visual hallucinogens, and an altered sense of time) and somatic (nausea, blurred vision and dizziness) (Lemke et al., 2013).

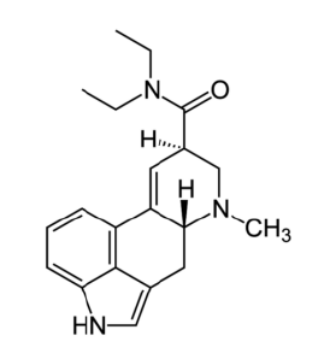

Figure 3: The chemical structure of lysergic acid diethylamide (LSD).

2.3 Phenylethylamine derivatives

As the name suggests, all phenylethylamine derivatives contain a phenyl, ethyl and amine moiety. Some examples can be seen in Figure 4. In terms of the biosynthesis of norepinephrine (NE) and dopamine they are all derived from the amino acid tyrosine.

The hallucinogenic compound mescaline which is found in the Peyote cactus, as well as amphetamine-like compounds such as cathinone found in *Catha Edulis* (also known as Khat) (Figure 5) are also structurally related to norepinephrine and dopamine and are also phenylethylamine derivatives. Amphetamine is an indirect-acting dopaminergic, serotonergic and norepinephrine agonist. The clinical applications of amphetamine-like compounds include obesity, narcolepsy and attention-deficit hyperactivity disorder (ADHD).

According to Hirst (2010) mescaline is really the champagne of the big four hallucinogens (LSD, psilocybin, and DMT). The mental clarity even at the height of visionary activity is

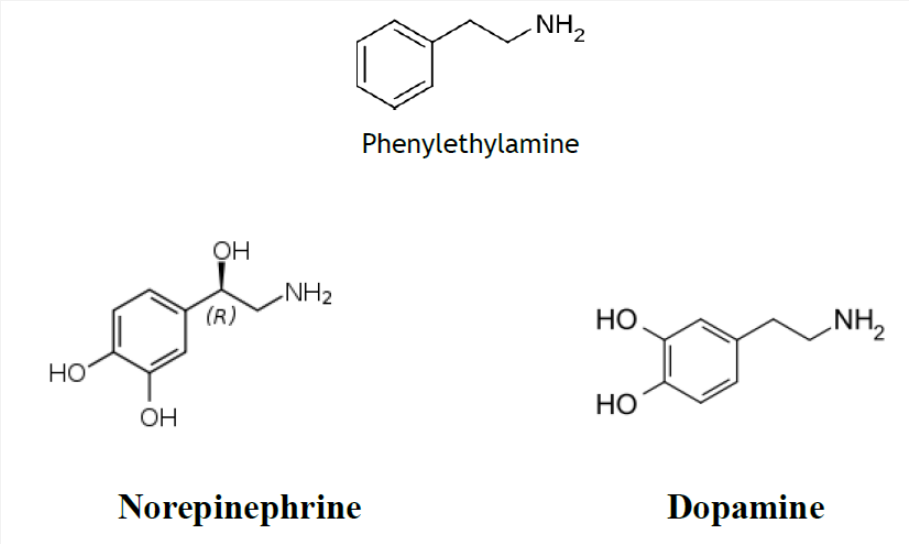

Figure 4: Phenylethylamine and its derivatives, norepinephrine and dopamine respectively.

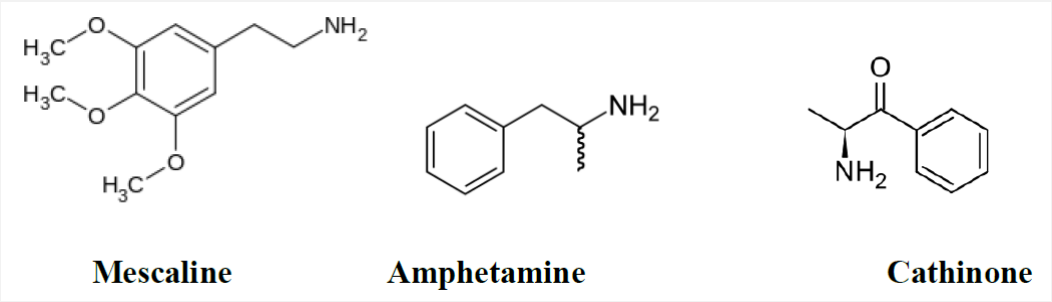

Figure 5: Phenylethylamine derivatives, mescaline, amphetamine and cathinone respectively.

amazing. Where acid/LSD tells one about one's place in the multiverse and blurs all the edges, mescaline tells one about the history of one's soul with such amazing visionary clarity.

Phenylethylamines represent the largest group of classical hallucinogens. In terms of SAR's, the α-methyl group increases the agent's lipophilicity and reduces its susceptibility to metabolism by MAO. Mescaline is a relatively weak hallucinogenic agent (total human dose approx. 350 mg). The introduction of an α-methyl group doubles the potency of mescaline (Lemke et al., 2013). In general the SAR's for amphetamine-like psychostimulant actions of phenylethylamines are quite distinct from the mescaline-like compounds, even though both share a common phenylethylamine structural skeleton. In general, incorporation of substituents into the aromatic ring of amphetamine reduces or abolishes amphetamine-like psychostimulant activity. While the addition of non-polar groups to the ring system increases hallucinatory mescaline type activity and decreases amphetamine like activity. Primary amines are more potent than the secondary amines, and the secondary amines are more potent than the tertiary amines, as general stimulants and hallucinogens. β-hydroxylation of amphetamine or hydroxylation of the aromatic ring results in decreased central stimulant actions. Increased polarity of the compound makes it more difficult to penetrate the BBB (Lemke et al., 2013).

The resemblance of phenylethylamines to dopamine and norepinephrine (NE), and tryptamines to serotonin, suggests binding to these areas, respectively. However, the complexity of these compounds suggests that they are able to bind to other systems as well. Thus a phenylethylamine can also bind to 5-HT systems, and tryptamines can also affect NE and dopamine (DA) systems. However, one feature that all the classical hallucinogens have in common is that they bind at the 5-HT_{2A} receptors (Lemke et al., 2013). Knowledge of the SAR's of hallucinogens and psychostimulants, makes it possible to legitimately forecast the actions and sometimes even the approximate potencies and adverse advents of designer street drugs. (Lemke et al., 2013).

2.4 Social engineering

The manipulation of SAR's to alter pharmacological activity lies at the heart of the designer concept. Many of the illicit street drugs intended to produce euphoria and enhanced awareness were developed based on an understanding of how specific modifications in chemical structure can lead to desired changes in both pharmacodynamics and pharmacokinetics (ADME). Unfortunately, although these approaches provide greater insight regarding the scientific basis of drug action, they are not without risk (Lemke et al., 2013). Inappropriate use has led to many fatalities, for example six amphetamine derivative fatalities were found in South Australia, and all individuals had histories of recent ingestion of illegal drugs thought to be Ecstasy (methylenedioxymethamphetamine, MDMA) at the time of purchase

(Byard et al., 1998). It is important to note that for every alteration in molecular structure intended for improved therapeutic efficacy and safety, there is often a parallel possibility of increasing abuse and toxicity (Lemke et al., 2013).

Could some medicines which are commonly used for a particular indication, also be used for other indications, at different dosages or during different circumstances? Social engineering and drug discovery can even entail the manipulation of old drugs for new tricks. Could already existing medicines be used as lead compounds to design better social engineering drugs? This could be achieved by "tweaking" a potential lead compound in order to improve the SAR's of the compound by moving or replacing key functional groups. This would alter receptor binding selectivity, which in turn changes the pharmacological actions of the compound (for better or worse).

For example, what lead compounds from phenylethylamine or tryptamine derivatives might be able to change or alter racial bias, low IQ, capitalism, extremism, pro-social behaviour, religious perceptions and longevity? The follow up ethical question to this would be, once these compounds have been discovered, how is it decided what values and beliefs are to be altered?

2.4.1 Ethics and philosophy

The main purpose of this paper was to examine the SAR's of selected phenylethylamine and tryptamine derivatives and their possible effects on society. As a result the ethical and philosophical aspects of social engineering have been acknowledged in this paper although there is still ample room for the further exploration of these topics.

According to Bilasová (2013), it is the responsibility of man to emphasise the need for constructive dialogue about ethics and to have a scientific responsibility in the context of present-day scientific discourses. The author further stresses the importance that the core mission of science should be that scientists are able to accept some form of responsibility for their work and that they are able to critically evaluate the ethos of their practice. The need to consider ethos in science is further highlighted when one considers William Ogburn's thesis, where he proposed that there is a fundamental conflict between the rate of development of modern technological advances and the much gradual pace at which ethical guidelines parallel to the uses of technologies are established (Marshall, 1999).

Most scientists with "good" intentions would quite easily accept the need for the assimilation of moral principles and a sound ethical philosophy in their work code when finding acceptable strategies to achieve suitable goals, especially if these goals are for the "greater good of Mankind". However, not all scientist operate from the same philosophical thinking regarding the topics discussed in this paper such as; enhancing cognitive functioning, racial

opinions and extremist behaviour etc., even if they believe themselves to be ethically considerate and morally just. This leaves the topic of socially engineering drugs open to a realm of unimaginable advancement for humankind or catastrophe and danger, depending on the outlook of the observer.

Aldous Huxley was quoted saying the following on the U.S State Departments Voice of America in 1961,

"*There will be in the next generation or so a pharmacological method of making people love their servitude and producing dictatorship without tears, so to speak. Producing a kind of painless concentration camp for entire societies so that people will in fact have their liberties taken away from them but will rather enjoy it, because they will be distracted from any desire to rebel by propaganda, or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.*"

Huxley's statement sounds either like an exaggerated idea or an imminent reality Mankind faces, yet one cannot overlook the possibility that social engineering drugs will provide Man with power. The power or control to socially engineer the way humans think, feel and behave can in fact give Mankind demi-god like qualities. According to Keltner et al. (2003) power is associated with, "positive affect, attention to rewards, automatic information processing and disinhibited behaviour". These associations are all constructive in nature and can reinforce feelings in Man to develop socially engineered drugs, if obtainment of power is an outcome. This is where one can expect an interplay between egoism and altruism (Spencer, 1879). If the requirement for power (or in other words egoism) overshadows the need for prosocial behaviour, one can expect to see nefarious outcomes.

In the 1960's Timothy Leary did research at the Harvard Psilocybin Project. A battery of experiments were conducted and psilocybin was administered to spiritual students to measure their divine experiences. Leary also tested psilocybin on convicts to see if they would stay out of prison after their release (Lopatto, 2011). Although Leary was dismissed from Cambridge Massachusetts campus in 1963, there was still a great rise in the usage of drugs amongst young people where he famously urged them to, "Turn on, tune in, drop out", with the use of LSD during the 1960's (Leary, 1999). Examining the Leary example, one can better understand how easily masses can be influenced to participate in something without having knowledge of the full extend or implications of their actions, as long as it feels good or is socially acceptable in a particular circle.

A good scientist would ask some and more of the following fundamental questions when considering the designing of social engineering drugs. Some of these questions would focus on the voluntarily or involuntarily usage of socially engineered drugs. What would be the legal age where a person could choose or be forced to take a particular drug? What about taking drugs during pregnancy? What are the long term implications to self and others and

society? One could just hope that if or when the day arrives where socially engineered drugs are used in areas as pointed out in the article, that Man and Society would appreciate the value of a moral and good ethos existing in self and at the workplace.

The subsequent drugs mentioned below are **not** cures, and their use is not being advocated in any way. In addition, some have potentially harmful side effects. However, at the very least, some of these compounds might be considered useful as lead compounds for further drug development and research experimentation.

2.4.2 Phenylethylamine derivatives as potential social engineering tools

Propranolol (Inderal®) is a β-blocker or β-antagonist (Figure 6). β-agonists such as salbutamol (Ventolin®) are classic phenylethylamine derivatives, while β-blockers are structurally but distantly related to β-agonists. β-blockers block the receptor instead of activating it. Propranolol reduces blood pressure and anxiety because it blocks the neurotransmitter norepinephrine, part of the body's stress response system. Small scale studies have shown that its calming effect also results in a lower score of subconscious racial bias. This implies that this drug or a closely related derivative might therefore be able to reduce the incidence of racial bias, at least at a subconscious level (Terbeck et al., 2012). More work still needs to be done on understanding the neurobiology of fear and racial bias.

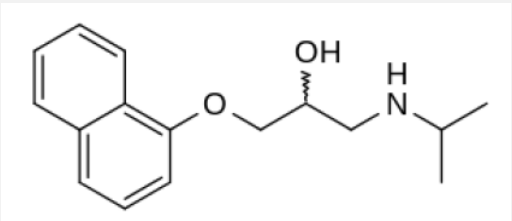

Figure 6: The chemical structure of Propranolol.

Modafinil (Provigil®) is a central nervous system stimulant whose mode of action has been attributed to dopamine and or norepinephrine increase (Figure 7). Modafinil has reduced stimulant character compared to methylphenidate. Modafinil is a phenylethylamine derivative, it has overall wakefulness-promoting properties and is commonly used to treat narcolepsy. Several studies have also shown that people who use this cognitive enhancer are able to concentrate and learn better and faster (Sandberg & Bostrom, 2006). Subjects who took an IQ test while using this drug performed significantly better than those without it. Interestingly, modafinil seems to work better on those with a lower IQ (Randall et al., 2005). American, French and British armies have shown a lot of interest in this drug (Estrada et al., 2012; Wesensten et al., 2005). There is a positive correlation in some Western society

between IQ and income and this raises a number of questions (Lynn, 2010). For instance looking at intelligence measures like the WAIS IQ test, what are the ethics involved with intellectual drug doping? Is the brain optimised for modern conditions? For example, numeracy and literacy versus hunter-gatherer societies?

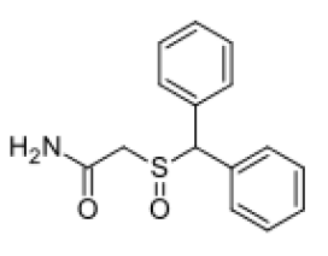

Figure 7: The chemical structure of Modafinil.

Methylphenidate (Ritalin®) is another phenylethylamine CNS stimulant drug and it is commonly used to treat attention deficit hyperactivity disorder (ADHD). Methylphenidate (Figure 8) can also be used as a concentration enhancer to meet the high demands of sustained attention in modern settings. Could methylphenidate or a closely related derivative be one of the drugs of choice in terms of increasing capitalist output and productivity by means of increased concentration and focus? Interestingly, depending on the circumstances, improved concentration does not necessary translate into improved cognition (Advokat & Scheithauer 2013).

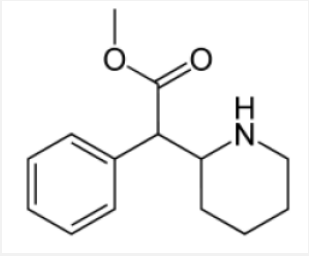

Figure 8: The chemical structure of Methylphenidate.

Lamotrigine (Epitec®) is a phenylethylamine derivative and an anti-epileptic drug which is also used as a mood stabiliser (Figure 9). This drug is used to treat bipolar disorders. Can certain kinds of extremism be called a mental illness? The short answer is yes according to some experts; extremism can be as a result of a borderline personality or a bipolar disorder both of which can be characterised by impulsive and sometimes psychotic behaviour (Derfel, 2014). Therefore, there exists the possibility that a mood stabiliser such as lamotrigine or a closely related derivative might be useful in the treatment of extremists.

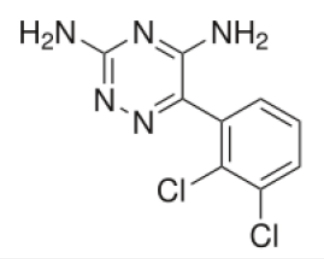

Figure 9: The chemical structure of Lamotrigine.

Oxytocin (Syntocinon®) is often referred to as the love or cuddle drug (Figure 10). This small nine amino acid peptide contains tyrosine (a phenylethylamine derivative). Small scale studies have shown that oxytocin has an impact on "pro-social behaviours" and emotional responses that contribute to relaxation, trust and psychological stability. In addition, studies have begun to investigate oxytocin's role in various behaviours, including orgasm, social recognition, bonding, and maternal behaviours (Magon & Kalra, 2002). Could oxytocin or a closely related derivative also be used to make our society more caring and less violent?

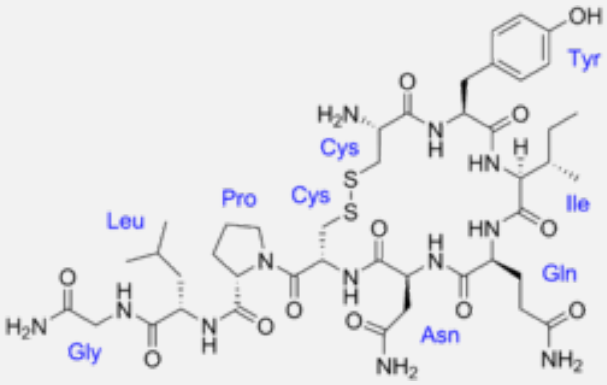

Figure 10: The chemical structure of Oxytocin.

2.4.3 Tryptamine derivatives as potential social engineering tools

Lysergic acid diethylamide (LSD) is noted to cause a spiritual awakening in some users. Some users of have confessed that they had a very profound mystical and unification experience with the environment and universe, similar to the "nirvana" experiences of Zen monks (Sayin, 2012). By opening up a world beyond our own, it is possible that atheists may rethink the existence of God and creation after taking this drug? Other tryptamine derivatives used

for religious ceremonies include psilocybin and DMT. Interestingly, LSD is unique in that it also has a phenylethylamine moiety. Indeed, some phenylethylamine derivatives may also be used for religious ceremonies such as mescaline. In the future, might it be possible to design drugs which increase or decrease religious feelings?

Melatonin (Circadin®) is another tryptamine derivative and a pineal hormone that is licenced for the short-term treatment of insomnia (Figure 11). Melatonin is also a potent free radical scavenger and its synthesis by the pineal gland declines with an increase in age. Thus, the protective effect of melatonin is slowly lost, making organs such as the brain more vulnerable to attack by free radicals. Considering stress, free radical damage and neuro-degeneration, daily supplementation with melatonin could be an option to delay such disorders and the ageing process (Limson et al., 1998).

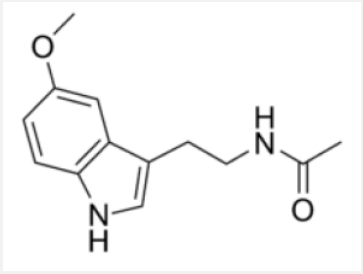

Figure 11: The chemical structure of Melatonin.

3 Conclusion

Exploring the chemistry of tryptamines and phenylethylamines is a fascinating journey into the heart of Man and Nature's existential inter-relationship. By improving/altering the SAR's of phenylethylamine related derivatives as well as tryptamine derivatives or by creating new phenylethylamine and tryptamine derivatives will certainly produce compounds with a wide variety of interesting and varied CNS pharmacological effects. Understanding how tryptamines and phenylethylamines interact with receptors and neurotransmitters in our CNS is critical, and is a fascinating area at the interface between chemistry and neuroscience.

This area still needs much better understanding through rigorous scientific research. This research would also assist Man in appreciating the role that these compounds play in determining the nature of our society, as well as assisting Man in understanding how these compounds could be used for possible social engineering purposes.

Acknowledgements:
Note: All chemical structures where copied from Wikipedia (Google images labelled for reuse) and cross referenced with Foye's Principles of Medicinal Chemistry.

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