RESEARCH ARTICLE

Mind the Gap: Bridging the Translational Gap in the Management of Schizophrenia by Treating the Whole Person.

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Abstract

Ever since the serendipitous discovery of the antipsychotic effect of chlorpromazine, the dopamine theory of schizophrenia has been the predominant one in both the understanding of its pathology and pharmacological management. Although this has had success in the management of positive symptoms of schizophrenia, this is not the case with negative symptoms of this disease. These are the ones which lead to the most long-term disability and consequent poor outcome. Pharmacological interventions for schizophrenia which concentrate on the dopaminergic pathways have had little success in alleviating negative symptoms of this disabling illness. Indeed, there has been a dearth of pharmacological initiatives addressing negative symptoms of schizophrenia.

Drug development seems to have been led by identifying and targeting a single explanatory mechanism for the disease. While each proposed explanatory mechanism has clear merits, each also has limitations. The most probable neuropathological explanation of schizophrenia is not confined to a single receptor or neural system, but the interaction of several dysfunctional ones. The especially aggressive nature of schizophrenia leads to a (variable) degree of cerebral tissue loss with each exacerbation of the illness. Understanding schizophrenia as a potentially neurodegenerative disease with neurodevelopmental antecedents may thus be a useful shift in the therapeutic appreciation of this illness. It is essential to remember that psychological and social factors also have neurological consequences: epigenetic influence is one way to understand the psychopathology of these consequences. This is, of course, the rationale for holistic treatment of the illness generally. The wide-ranging pathology of schizophrenia means that holistic management of it will always be required and the concentration on a single pathological pathway is one which both leads researchers to unrewarding conclusions and results in an unsatisfactory outcome for the person who suffers from schizophrenia. Successful management of this illness is therefore always holistic, including the maintenance of appropriate suitable medication as well as psychological and social interventions which are recovery focussed. A thorough understanding of all of the factors involved in schizophrenic illness therefore narrows the translational gap.

Introduction

We are fortunate to be living in a time when the understanding of illness is far more sophisticated than in previous eras. This allows us to more accurately target management efforts for an illness. These can be very well illustrated when considering the management of schizophrenia.

The biological understanding of schizophrenia could be said to have begun when the calming effect of Chlorpromazine was serendipitously noted by Jean Delay, Pierre Deniker and Jean Marie Harl in Paris. Delay was the head of the neurological facility at the Hôpital Pitié-Salpêtrière. Together with his assistant Pierre Deniker and their associate JM Harl, the calming effect of Chlorpromazine was noted in people to whom this was given as a peri-operative anti-emetic. The marked reduction in anxiety in such people eventually led to the investigation of this substance's efficacy in the mental illnesses. The dramatic improvement in the symptoms of people with schizophrenia when given Chlorpromazine led to what has become known as the 'unlocking of the asylum doors '. Thus began the revolution in the understanding and treatment of the severe mental illnesses. This understanding is continually evolving and will be further considered in subsequent sections here. There is a variety of classes of new drug treatments being investigated for schizophrenia. This piece, necessarily, cannot cover them all. Here, the concentration will be on the nicotinic receptor enhancers, to illustrate particular points about antipsychotic drug development.

Other agents are always being investigated as medications for the serious enduring mental illnesses. One such group of agents is the nicotinic receptor enhancers, which have relatively recently been investigated for the amelioration of negative symptoms of schizophrenia. As indicated here in the abstract, pharmacological interventions for negative symptoms of schizophrenia are extremely rare. As negative symptoms of schizophrenia are the most disabling, there has been great interest in the nicotinic receptor modulators as possible treatments for these. This class of drugs will be further discussed below. Other agents in pharmacological development, such as the positive allosteric modulating agents, or glutamatergic agents will not be considered in this brief piece. The nicotinic agents are examined here to illustrate the distance of the translational gap between laboratory and bedside.

The further biological understanding of schizophrenia, from a histological and functional viewpoint, has undoubtedly benefited from the exponentially successful advances in neuroimaging since the 1980s. Similarly, advances in neurophysiological modelling have allowed a more detailed appreciation of the pathology of schizophrenia. While several neurotransmitter systems have been implicated in the pathogenesis of schizophrenia, the *final common pathway for expression of symptoms* is via dopaminergic over-activity (Howes and Kapur 2009). The dopamine pathway is also operative in other acute mental illnesses, such as hypomania; this leads to the wide spectrum of illnesses which dopamine-antagonising antipsychotics are effective in. [Wryly, this is an explanation for the former pejorative appreciation of psychiatry by other medical specialists as 'only having one drug !'] This is because dopamine antagonists can be used for acute presentations of several differing illnesses, such as acute schizophrenia and acute (hypo)mania. Indeed, an acute episode of schizophrenia and an acute hypomanic episode can be difficult to distinguish at first glance: this is a clinical illustration of the final common neurological pathway for these

acute illnesses. All of the drugs which are successful in alleviating acute symptoms of schizophrenia have some level of antagonism at the dopamine D_2 receptor and their antipsychotic potency is proportional to the degree of antagonism here (Yang and Tsai 2017). Howes and Kapur sensibly state that future drug development would be better focussed on factors upstream from the dopamine pathway. Certainly, there has been much investigation into potential neurotransmitter candidates. None of these systems fully explain the heterogeneity of symptoms in schizophrenia. Andreasen in 2008 very reasonably states that the so-called unitary model of schizophrenia – i.e. the elusive single explanatory mechanism for the illness is, to quote, "...a fundamental cognitive deficit that arises from *multiple abnormalities in neural circuits*" (my emphasis). This quote declares that the abnormalities are in *multiple* circuits and expresses how the pathological process of schizophrenia is one which has wide-ranging cerebral consequences. The singularity of an explicatory model is far better understood as Andreasen's "fundamental cognitive deficit" (2008).

Difficulties with rodent modelling

Another of the difficulties when trying to bridge the translational gap is the use of rodent systems for modelling of and subsequent investigation into abnormalities in the physiological pathway that leads to the manifestation of schizophrenia. While rodent systems can be very useful for identifying the neurophysiological basis of illness and potential therapeutic agents, they are less useful for later stage drug design. To quote:

"Additional attention must be paid to species differences both in terms of receptor function and differences in neuronal networks." (Bertrand and Terry 2018)

And -

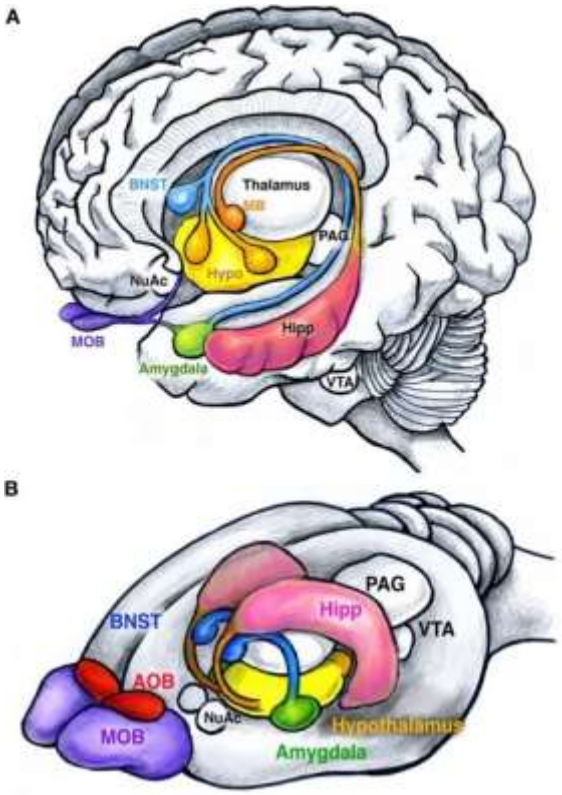
"... most of the efficacy assessments are made in rodent models, a particular limitation since the behavioural repertoire of rodents is quite limited compared to humans. … short-term experiments in animas with a high drug concentration are not the same as long-term exposures with a low concentration in humans" *(ibid).*

Therefore, rodent modelling may be one reason for translational error in drug design. While neurophysiological mechanisms can be best understood in a whole, living organism, the initial studies can conceivably now be performed in laboratory-generated tissue cultures.

As noted above, rodent models have their limitations when schizophrenia is being investigated. Of course, the linguistic abnormalities inherent to this disease can never be investigated in a rodent system. Similarly, elicited behavioural patterns are understood as analogues to schizophrenic symptoms, such as reduced exploratory behaviour, or impaired problem-solving in a standardised rodent behavioural task. For example, Manetti *et al* (2018) mention the *mouse passive avoidance test* as one of these behavioural analogues. These models, inevitably, can only be approximate analogues to the constellation of schizophrenic symptoms seen in a human sufferer of the disease. Rodent modelling may, therefore, be another reason for translational error in drug design. The utility of experimental animal models is in identifying candidates for the potential neurophysiological mechanisms of an illness, and thus of the pharmacological agents used to treat it. To reiterate, the behavioural analogues used in investigation are necessarily only approximations. While neurophysiological mechanisms are best understood in a whole, living organism, initial studies can conceivably now be performed in laboratory-generated tissue cultures. Doing so may lead to a slightly

reduced use of rodents in the initial stages of drug design.

Later stages of drug design will involve assessing the behavioural modifications, if any, caused by the compound being investigated. Again, there is a problem when designing a new drug for schizophrenia. If a research group is trying to ascertain the possible behavioural benefits of a compound in schizophrenia, the animal models of this condition are necessarily limited, as implied above. While laboratory rats bred to exhibit a specific behavioural phenotype could be said to be relatively homogenous in their neurophysiology – and therefore useful in investigating the biochemical pathways in the illness – again, their limited behavioural repertoire may be one of the reasons underlying the translational gap between laboratory and bedside. For example, psychostimulant-induced locomotion in rodents has been used as the animal analogue for positive symptoms (Kesby *et al* 2018) and has been found to be associated with dopaminergic overactivity in the rodent limbic striatum. This problem is rather difficult to appreciate without illustrations.



Kesby et al (2018) state that dopaminergic excess does not occur primarily in the human limbic system, but in the dorsal portions of the corpus striatum. This is at variance to rodent cerebral function, where the limbic system has been found to be more important in behaviours analogous to human schizophrenia.This,practically, illustrates the point made by Bertrand and Terry (2018) aboutinter-species specificity.

Fig i – A) Human and B) Rodent limbic systems *from Sokolowski and Corbin 2012.*

In the rodent brain, the *associative striatum* is chiefly the dorsomedial area of the striatum and the *ventral tegmental area* (VTA) is of greater significance in the initiation of goal-directed behaviour. Of course, the far larger frontal cortex of the human (and primate) brain is the main source of goal-directed behaviour and the initiation of action in these organisms. This implies that the human brain is far more susceptible to both external and internal influences on behaviour due to the differing pattern of

functional connectivity. *Magnetic resonance spectroscopy* (MRS) is an appropriate mode of investigation of the circuitry involved in a living subject. The number of MRS studies conducted in patients with schizophrenia is small and it is impossible to perform an MRS study in a person who is acutely ill with this disease. Stable out-patients are the most usual subjects for this type of study and the findings thus obtained remain informative for understanding the general pathology of the illness.

It perhaps should not be too surprising that there is inter-species differentiation in dopaminergic innervation and in the relative importance of each cerebral area. However, the gross physiological divisions are broadly analogous in mammals, which is what potentially permits animal modelling. The interpretative – and thus, translational – error lies in attempting to understand specific neurological final pathways. These may well be species-specific, as implied in the above illustrations.

The search for a 'magic bullet'.

Several researchers devoted their energies a few decades ago to searching for 'the gene for schizophrenia'. Relatively recently, this was thought perhaps to be the locus of the α7 nicotinic receptor gene, CHRNA7, at locus 15q 14 (Leonard *et al* 2000). It is now very clearly apparent that while some genes can have a large impact on phenotypical schizophrenia, this is a multifactorial illness. Therefore, i is probable that multiple genes and mechanisms combine to ultimately manifest as clinicl schizophrenia. The search for candidate genes stemmed from the fact that schizophrenia has a strong genetic component to its phenotypical appearance. However, two very thorough studies, in 2008 (Sanders *et al*) and 2017 (Johnson *et al*) found that proposed candidate genes did not show a significantly greater association with manifest schizophrenia. It is important to remember epigenetics (very briefly discussed below) which can go a long way towards explaining differences between genetically similar individuals. Epigenetic phenomena also, perhaps, account for the variation of effect in expressed schizophrenia candidate genes. These epigenetic mechanisms can include factors such as cigarette smoking, ingestion of alcohol or illicit substances, stress, diet, exercise... Again, this is an indication of the utility of the holistic method of illness management. To further illustrate the importance of epigenetic factors, the particular example which will be concentrated on here is tobacco cigarette smoking in schizophrenia. When tobacco cigarettes are smoked, the aryl hydrocarbons in the cigarette smoke induce hepatic catabolic enzymes. Therefore, a schizophrenic smoker requires a higher dose of antipsychotic medication. Cigarette smoking also results in an up-regulation of nicotinic α_7 receptors (Brown *et al* 2013). These receptors have a low sensitivity and thus need higher doses of nicotine to become activated (Leonard *et al* 2000). Further, people with schizophrenia have decreased numbers of hippocampal nicotinic receptors and so again require higher doses of nicotine to become sufficiently activated (Freedman *et al* 1995). This is another factor in support of the *self-medication theory* – mentioned below – where people with schizophrenia smoke as heavily as they do to compensate for their reduced level of nicotinic cerebral activation. At the hippocampus, this leads to impaired sensory gating, which can manifest as positive symptomatology in schizophrenia (Freedman 1995, Conway 2016).

Perhaps what makes a particular theory so attractive to its proponents is the way in which so many other aspects of the schizophrenic illness can be explained by reference to the theory under discussion.

However, it is becoming clear that no one neurotransmitter explanation can encompass all of the difficulties caused by this illness. As Kondej et al (2018) point out, "...it is necessary to go beyond the 'magic bullet' concept." The only pharmacologically correct management of schizophrenia, as implied above, is a holistic one: this consideration necessarily correctly unifies biological, psychological and social therapeutic efforts.

Pathogenesis of negative symptoms and their influence on illness behaviour

These mechanisms are all upstream of the final common pathway of an acute exacerbation of schizophrenia, I.e. cerebral dopaminergic overactivity (Howes and Kapur 2009). It is notable that although negative symptoms are the most disabling in schizophrenia leading to the greatest illness cost – both literal and metaphorical – the level of research into negative symptoms of schizophrenia pales into insignificance compared to potential alleviation of positive symptoms (Veerman, Schulte and de Haan 2017).

A potential explanation for negtive symptoms in schizophrenia and thus, potential therapeutic target was outlined as the *glutamatergic mechanism.* This was most clearly stated initially by Olney, Newcomer and Farber in 1999. Here, antagonism at the N-methyl-D-aspartate (NMDA) receptor system leads to a neurophysiological state defined by these workers as *NMDA receptor hypofunction*. Reduced functioning in the NMDA receptor system leads to reduced activation of inhibitory pathways. The resultant neural overactivity is what leads to the clinical presentation of an acute exacerbation of schizophrenia. Glutamatergic over-activity is seen in several cerebral areas before a first psychotic episode (Olney, Newcomer and Farber 1999 and Chiu *et al* 2018). This also leads to excitotoxic cell damage because of the unremitting neural excitation caused by NMDA receptor hypofunction and the consequent unremitting release of the excitatory neurotransmitter glutamate (Jarskog 2006). Rather like increased dopaminergic activity being a common factor in several pathways, tissue loss resulting from excitotoxicity is another feature common to the many explanatory pathways of schizophrenia. It is another downstream feature of schizophrenic neuropathology. This is all eloquently explained by Jarskog (2006). There is no glial scarring, as found in (other) neurodegenerative illnesses, because of increased cerebral microglial activity in schizophrenia. Cerebral microglia can be best understood as central macrophages, which catabolise non-functional neurocytes. If the over-excitative process is prolonged, cerebral neurones become depleted of their transmitter content and thus non-functional. As a result, they will be catabolised. Therefore, consequent tissue loss is marked and is evident morphologically as sulcal widening and thinning of gyri in the brain (*ibid*). Tissue loss in schizophrenia has been noted for very many years: indeed, one of the earliest understandings of schizophrenia was as 'dementia praecox', by Kraepelin and later by Bleuler in the early 20th Century: cerebral tissue loss was later found to be a feature of this group of illnesses. The tissue loss was, much later, found to be essentially proportional to the level of cognitive disability in an affected young person, hence 'dementia praecox'.

The apoptotic cell loss caused by excitotoxicity is what eventually leads to cerebral sulcal widening and gyral thinning. A difficult problem in the management of schizophrenic illness, particularly with the negative symptoms, is that the first onset of the illness may impair the affected person's search for help. In people who are perhaps

more (dysfunctionally) motivated, substance misuse may be resorted to in an attempt to alleviate often frightening psychotic symptoms. Of course, a potential unfortunate consequence of this mode of attempted remedial action is the worsening of pre-existing symptoms, especially persecutory experiences and beliefs, when high-potency 'skunk' cannabis is ingested. This type of cannabis is the most widely available variant currently (2019). All cannabis in the UK is obtained from illicit sources and the production and sale of cannabis currently concentrates on the high-potency 'skunk' variety, which has a much higher tetra-hydro cannabinol (THC) content. Higher THC content leads to more persecutory feelings in the person who ingeststhis form of cannabis. Of course, in a person who is already unwell with (even incipient) schizophrenia, this is very dangerous.Therefore, positive symptoms become the factor in this casw which precludes therapeutic contact. In other affected people, the first onset of illness may be associated with profoundly negative symptoms: these will have the effect of (further) reducing the person's social interaction and thus causing a longer duration of untreated psychosis (DUP). Therefore, primary negative symptoms can cause a longer DUP, especially with an early age of onset and an insidious progression of features of the illness. A preponderance of primary negative symptoms implies a more aggressive illness pathology and a worse prognosis. This is why the length of DUP correlates with the worsening of prognosis. When applying a holistic consideration to the problem of first-onset schizophrenia, the social consequences of self-medication with illicit drugs would very probably discourage the affected person from seeking help. Not only would the affected person be frightened by their emerging symptoms, the people acting as the sources of illicit substances would be far more likely to be distanced from, and antipathetic to, statutory agencies such as health service clinics. They could then negatively influence the person suffering from emerging schizophrenia, increasing the affected person's distance from therapeutic teams.

As well as the excitotoxic tissue loss caused by NMDA hypofunction leading to excessive cerebral glutamate levels, another responsible mechanism is a reduction in central gamma-amino butyric acid, GABA (Chiu *et al* 2018). The reader is reminded that glutamate is the most important excitatory cerebral neurotransmitter, while GABA is the most important inhibitory cerebral neurotransmitter. Chiu et al's detailed spectroscopic studies implied both decreased neuronal inhibition and increased neuronal turnover *in first-episode schizophrenia* subjects. Their study reminds us of the aggressive pathological process which underlies the schizophrenic illnesses. Remembering Andreasen's declaration (2008) that the phenotypic expression of a schizophrenic illness is the result of the interaction of multiple disrupted mechanisms, reduced nicotinic receptor activity can also lead to reduced GABA release. When this occurs in area CA3 of the hippocampus, it leads to impaired sensory gating (Conway 2016) and so elicits positive symptoms. Here, a reduction in cerebral GABA may be a result of inherent reduced synthesis – this being genetically determined - leading to excessive glutamate release, with consequent excitotoxicity. The glutamatergic pathways of schizophrenia necessarily include GABA transmission further upstream. GABA release in inhibitory inter-neurones will modulate post-synaptic glutamate release. Hence, there is a finely tuned balance between neural inhibition and excitation. A disruption of this balance can lead to a pathologic manifestation of symptomatic mental illness.

While excessive glutamate release can become pathogenetic, for example in acute presentations, in other phenotypic instances of schizophrenia, such as the deficit state, glutamatergic potentiation is being investigated as a potential treatment for negative symptoms.

Potentiation at cholinergic pathways was first looked at in detail when possible pharmacological managements for Alzheimer's disease began to be investigated. Part of the efficacy of drugs such as donepezil or rivastigmine had been attributed to the nicotinic activity of these drugs. - They were found to improve cognition and delay the progression of cognitive impairment in Alzheimer's disease (Takeda *et al* 2006). It was recognised that these mechanisms might also be useful in the management of schizophrenia, for the same reasons that they were investigated in Alzheimer's for: to address the impairment of cognitive function -here, *the negative symptoms of schizophrenia*. There has been a large body of work investigating this neurological pathway which had led to the development of nicotinic receptor activating drugs such as Encenicline and Bradanicline for schizophrenia.The excitement around this group of drugs was that they could, at last, begin to address the considerable disease burden of negative symptoms on schizophrenia. As mentioned above, Veerman, Schulte and de Haan (2017) cite the dearth of research into management of negative symptoms of schizophrenia. Similarly, they express an understandable despondence at the lack of research into negative symptoms. They note the paucity of work on primary negative symptoms as opposed to secondary negative ones, caused by the cerebral damage induced by acute exacerbations of the illness. Unfortunately, later phase trials of nicotinic acetylcholine receptor modulators have proved to be disappointing. During phase III trials, substances such as Encenicline and Bradanicline were found to have intolerable gastro-intestinal side-effects. This is a consequence of the wide somatic distribution of nicotinic receptors and their consequent involvement in several physiological processes. It is particularly unfortunate that a class of agents which were, theoretically, so promising, failed at their final pre-clinical step. This is yet another instance of the translational gap between laboratory and bedside.

Epigenetic mechanisms in schizophrenia

Tobacco cigarette smoking is an excellent example of an epigenetic mechanism. Epigenetic modifications also include things like DNA methylations or modifications of the regulatory histone proteins in the nucleosome. These chemical events alter the expression of the genetic code without altering the DNA sequence (Peng and Zhong 2015). Acetylation at histones in the nucleosome can affect, for example, the folding properties of expressed protein products coded by the cell's DNA. If these protein products include membrane proteins, the sensitivity to ligand binding or ionic channel permeability is altered. Therefore, important aspects of cellular – and thus, neurological - function are altered without any alteration to the underlying genetic code.

It has been mentioned above that inhalation of cigarette smoke causes increased catabolism of antipsychotic drugs, via induction of the cytochrome P450 group of enzymes. There is a very large body of work investigating the link between smoking and schizophrenia – which later progressed to investigation of the link between nicotine and schizophrenia (Freedman, Hall, Adler and Leonard 1995, Olincy, Young and Freedman 1997, Dalack, Healy and Meador-Woodruff 1998, Rezvani and Levin 2001, Kumari and Postma 2005). Several research

groups in the USA have noted that there is an improvement in cognition after ingestion of nicotine (e.g. Rezvani and Levin 2001). Unfortunately, the most efficient mode of delivery of nicotine remains via inhalation of cigarette smoke. It is well-recognised that people with schizophrenia smoke at a far higher rate than the general public and at a far higher rate than their peers with other mental illnesses (Olincy, Young and Freedman 1997). There is every reason to infer that this increased consumption rate is biologically driven – people with schizophrenia are attempting to self-medicate their deficient cerebral nicotine levels (Dalack 1998, Kumari and Postma 1999). However, more recently, doubt has been cast upon the self-medication hypothesis (e.g. Wang *et al* 2019). Wang *et al* draw attention to the fact that several issues limited their meta-analysis of cognitive effects of smoking in schizophrenia: not least of these were the relative lack of comparable data, variable strictness of diagnostic groupings of study subjects, and the lack of control subjects in several studies. To definitively answer this question, Wang *et al* reasonably state that prospective studies need to be undertaken on cohorts of people with schizophrenia who are smokers and non-smokers. It should not be too surprising that an experimental trial has not been undertaken where part of the subjects are required to smoke cigarettes so that their neurological effects can be investigated. The cardio-respiratory dangers are far too high for such a study to ever be ethically approved.

We are in a fortunate period now, where e-cigarettes have become a socially acceptable alternative to tobacco cigarette consumption. E-cigarettes are generally acceptable to the person consuming them too. Of course, because we are still in the early stages of e-cigarette use, there is no longitudinal data on the cumulative cardiovascular or respiratory effect of these: perhaps one of the main unanswered questions is the longitudinal cardio-respiratory effect of solvent inhalation. This consideration refers to the flavoured solvents that can be inhaled together with nicotine by the person using an e-cigarette.

There are very recent (2019) concerns about the safety e-cigarette use, after multiple deaths in the United States and one in the United Kingdom. All of the fatalities in the USA occurred when e-cigarettes were used to consume cannabis - and thus, the e-cigarettes were illicit ones. The gentleman who died last year in the UK purchased his final e-cigarette online. Thus, certainly in the American cases and most probably in the British one, the e-cigarettes used were prepared illicitly. The UK Department of Health's advice remains that e-cigarettes from reputable sources are 95% safer than tobacco cigarettes.

Influences of research on the everyday management of schizophrenia on the psychiatric ward

The pragmatic implications of this body of research lead to more prosaic management changes for in-patients with schizophrenia. For example, when a person is admitted to a psychiatric hospital in the UK under the provisions of the Mental Health Act, one factor apart from the person's acute symptoms that impairs engagement with the treating team is the inability to smoke cigarettes on the hospital ward. At its worst, the resultant discomfort of the patient concerned may lead to violent altercations. Quite apart from the evident disruption to the person and staff team concerned, the stress of such an event has physiological consequences: the associated release of cortisol in the affected person's system is neurotoxic (Qin *et al* 2016, Uno *et al* 1994). However, the availability of e-cigarettes for in-patients would allow the

affected person to ingest exogenous nicotine in a far less harmful way than via tobacco cigarettes. One source of stress is therefore removed for the affected person. As there would not be any induction of hepatic cytochrome P450 enzymes, the affected person would also not require the higher dose of antipsychotic medication that people who smoke do. Therefore, provision of e-cigarettes could lead to, ultimately, improved engagement with the treating team. Allowing an affected person to consume e-cigarettes may alleviate at least some of the discomfort of compulsory admission. As a potentially lower dose of antipsychotic medication would be needed in the acute phase, the person would be less liable to side-effects. This is important, because it could be an element of management which promotes long-term compliance with antipsychotic medication. As implied above, the resultant reduction in acute exacerbations will necessarily reduce the level of tissue damage caused by excitotoxic cell loss. Hence, the longer-term prognosis is also improved. There are, therefore, multiple benefits to allowing the use of e-cigarettes in an in-patient environment. These prosaic benefits also have a solid neurochemical basis. Schizophrenia is an illness with such an aggressive pathology that the establishment of an early solid therapeutic alliance can very usefully optimise the prognosis for the affected person. By improving engagement with a therapeutic team and compliance with antipsychotic medication, the cerebral damage caused by repeated exacerbations of schizophrenia is potentially minimised. Wang *et al* reasonably state that to answer the question about self-medication more definitively, prospective studies need to be performed to determine whether cognitive function actually is improved by ingestion of exogenous nicotine. Now that e-cigarettes are widely available, these would provide the ideal delivery device for the exogenous nicotine (Hickling *et al* 2018). It is very possible that this issue has not been settled previously because there were no alternative devices to tobacco cigarettes for the delivery of exogenous nicotine.

In conclusion therefore, there is a large body of work which supports the symptomatic influence of nicotine in schizophrenic illness. While there have been disappointing findings when some of the potential pharmacological agents have been investigated in detail, there are other possible pragmatic agents which could be clinically useful. The most obvious of these, as implied above is the e-cigarette. There is room for prospective work on the utility of e-cigarettes in people with schizophrenia. The theoretical background leads to the conclusion that nicotine has a role in enhancing neuro-inhibition, particularly in the hippocampus, while the pragmatic implication of this body of work is that e-cigarettes have a validity in the adjunctive management of schizophrenia, especially where sufferers of the illness have a high level of cigarette consumption. Further work is definitely indicated here: both negative and positive results of such work will be informative for the further understanding of the pathology of schizophrenia and the search for effective remedies for this illness. Such work will, potentially, narrow the translational gap.

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