

Nicotine and symptoms of schizophrenia: the 2017 picture

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Abstract

The tendency of people who suffer with schizophrenia to consume large amounts of cigarettes and to extract more nicotine from these cigarettes is well-known. A sizeable body of work investigating this has concluded that smoking in people with schizophrenia improves the dysfunctional sensory gating intrinsic to this disease. This has been recognised at least since the late 1980s. Consequently, the pro-cognitive effect of nicotine is now well-recognised and has led to the investigation of nicotinic receptor modulators as potential treatments for schizophrenia. Particular interest has focused on the treatment of negative symptoms in this illness. While there is a solid theoretical basis for this line of drug development, in practice, later-stage drug trials of compounds such as TC-5619 (bradanicline) in Phase 2 and EVP-6124 (encenicline) in Phase 3 have been disappointing. Numerous intolerable side-effects have been important in limiting the clinical use of such compounds. It is conceivable that the reason for intolerable side-effects might be a consequence of the wide distribution of nicotinic cholinergic receptors: α_7 nicotinic receptors are found in several cerebral areas, in the spleen and in lymphocytes at lymph nodes.

Later-stage drug development trials which reveal insurmountable administration problems are perhaps indicative of the great practical distance between theoretical recognition of a potential therapeutic agent and its eventual translational appearance in the armory against an illness. Given that this is the case it may still be worthwhile to look at the simple administration of exogenous nicotine via e-cigarettes or chewing-gum as an adjunctive agent in the treatment of schizophrenia in the interim. More prosaically, the banning of smoking in many hospital premises in the UK has led to a difficulty in the practical management of acutely ill people with schizophrenia in the in-patient setting. In a group of people who are profoundly psychiatrically unwell, and often physically compromised to some degree because of their cigarette consumption, alternative management techniques for the latter must be explored. Use of exogenous nicotine replacement in a less harmful delivery manner than cigarettes in a group of people who have a clear physiological reason for smoking -i.e. to increase their deficient endogenous cerebral nicotine levels – is worthwhile to investigate. Very recent work in exactly this direction has been undertaken. Nursing management of such patients may be greatly improved as a result, as may their on-going engagement with the therapeutic team. Here is an illustration of how theoretical considerations eventually come to have a pragmatic consequence in the day-to-day management of people with severe and enduring mental illnesses like schizophrenia.

Background: the neuropathology of schizophrenia

The increased tendency of psychiatric in-patients to smoke is well-known. Explanations for this used to focus on the ward lifestyle. Even as recently as 2006, the association between admission with schizophrenia, smoking and high dose of antipsychotic medication was being reported in Finland (Salongkas *et al* 2006). When associations such as this are consistently found, it is imperative to investigate the reasons for the association. It must always be remembered that correlation is not the same as causality. While a correlation gives a clue to the possible causal mechanism, it is not the full explanation. It has consistently been found that habitual smoking is far more pronounced in people suffering from schizophrenia: 76 to 88% of schizophrenic patients (e.g. Kelly *et al* 1999, Patkar *et al* 2002). This topic began to be deliberated upon in the 1970s and 1980s. Another relevant aspect was eventually found to be the fact that the aromatic hydrocarbons in cigarette smoke induce catabolic cytochrome enzymes (Zevin and Benowitz 1999, Desai *et al* 2001). As such, heavy cigarette smokers – those who smoke more than ten cigarettes per day – require higher doses of psychotropic drugs. People who smoke at this level sustain nicotine levels (as measured by serum levels of its metabolite, cotinine) of 5ng/ml trough up to 35ng/ml peak (Hong *et al* 2011). In non-smokers, serum cotinine levels approximate 3ng/ml (Benowitz *et al* 2009). Therefore, those who smoke more than ten cigarettes per day have a consistently higher circulating nicotine level. In people who suffer from schizophrenia, it is worthwhile to examine the reasons for their increased cigarette consumption. The higher circulating nicotine level affords a clue to the explanation.

When first-generation antipsychotic drugs were commonly used in the in-patient environment, it was reasonable to believe

that part of the reason for the heavy consumption of tobacco cigarettes was the drive to lower the level of serum antipsychotic to decrease the occurrence of extra-pyramidal side effects. The hepatic catabolic process for psychotropic drugs has been further detailed and confirmed. As has been stated above, constituents of cigarette smoke- namely, the aromatic hydrocarbons - induce the hepatic cytochrome enzymes which break down several drugs and toxins, and this is completely independent of the nicotine component of the cigarette (Benowitz 1999, Desai *et al* 2001). Tobacco cigarette consumption therefore needs to be taken into account when prescribing for a person who has schizophrenia. The second-generation, atypical antipsychotic medications have far less incidence of extra-pyramidal side effects but the incidence of smoking in people with schizophrenia remains markedly raised: the figure remains up to eighty-eight per cent, as has been mentioned above. It was therefore clear that the reasons for smoking in schizophrenia are not simply due to in-patient lifestyle, for example. McEvoy and Brown (1999), amongst others, have suggested that smoking is a marker for the more severe forms of schizophrenia. A tremendous body of work has become established on the topic of smoking, nicotine and schizophrenia and has been investigated via numerous methods.

At this point, the role of the tobacco industry must be mentioned. In 2008, Prochaska *et al* looked at the influence of the companies who sell tobacco in the USA on tobacco use policies in healthcare there. They found that these companies actively promoted the susceptibility of people with schizophrenia to smoke and actively worked against smoking bans in hospital setting in the USA. Prochaska *et al* examined many documents which were previously secret to uncover the actions of these companies. These corporate actions are clearly unfortunate: the single-minded pursuit of

financial advantage by the businesses concerned has thrown some unnecessary confusion into a valid body of work that investigates the neuropathology of schizophrenia.

Sensory gating in schizophrenia

Electrophysiological changes in people who suffer from schizophrenia have been demonstrated to be a useful method of investigating the neurophysiological mechanisms involved.

A robust finding in schizophrenia is the lack of pre-pulse inhibition. Pre-pulse inhibition is an electrophysiological investigation of sensory gating: this refers to electrophysiological measurement of cerebral activity when sensory stimuli are presented in rapid succession. There are numerous articles on this topic, such as Braff *et al* (2001) which describe the investigatory process. In the well-known two-click paradigm, a stimulus noise is presented against a background of white noise: the stimulus is generally a loud click. The cerebral response to this sensory stimulus is measured by electroencephalography. If a second clicking noise is presented soon after – for example 50 milliseconds or 300 milliseconds later, the evoked response potential at the cerebral vertex is found to be of a lower amplitude both in people who suffer from schizophrenia and in their first-degree relatives. This is described as P50 or P300 *pre-pulse inhibition*. This is said to be indicative of sensory gating: cerebral activity is maintained towards the first stimulus until neurological processing of it has been completed. Potter *et al* (2006) also describe sensory gating as “...the pre-attentional

habituation of responses to repeated exposure to the same sensory stimulus.” The fact that both people who suffer from schizophrenia and their first-degree relatives show a lack of pre-pulse inhibition demonstrates a possible liability to this illness. However, additional hippocampal pathology is necessary before the potential sensory gating deficit becomes manifest in a psychotic state (Dalack *et al* 1998, Adler *et al* 1998). It is also probable that the hippocampal pathology must be long-standing. It is well-recognised both clinically and in the research setting, that in first-episode patients, a longer duration of untreated psychosis is associated with a far less favorable prognosis. This is most probably due to the establishment and reinforcement of dysfunctional cerebral circuitry. Attentional deficits are also found in sustained attention in schizophrenia. Hong *et al* (2011) investigated sustained visual attention here and found a “...trait-like deficit...across early and chronic states of the disease in medicated and never medicated individuals”. This group of researchers noted that exogenous nicotine can also transiently improve sustained attention in people with schizophrenia. This confirms the work of Adler *et al* in 1998, who investigated P₃₀₀ pre-pulse inhibition. The deficit in sensory gating, i.e. the loss of pre-pulse inhibition, has been traced to reduced action at α_7 nicotinic cholinergic receptors: here, exogenously-administered nicotine could only transiently restore pre-pulse inhibition for up to thirty minutes and the improvement could not be sustained. This is most probably because the neural receptor involved, the α_7 nicotinic receptor, is one which desensitises quickly.

The role of the α_7 nicotinic cholinergic receptor

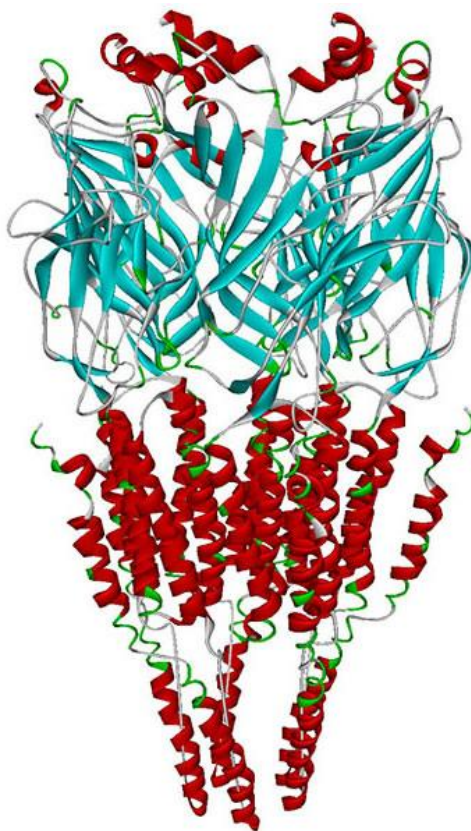


Figure 1. Molecular model of the α_7 nicotinic cholinergic receptor
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The molecular model illustrated here permits visualisation of the pentameric receptor structure, which here comprises five homogenous α_7 molecules. Other nicotinic receptors are heterogeneous, such as the structure, which contains two types of constituent molecule: α_4 and β_2 ; this receptor has three β_2 and two α_4 molecules. $\alpha_4\beta_2$ receptors are involved in cerebral meso-limbic projections. They modulate behavioural reinforcement and so are operative in the addictive properties of nicotine and thus of cigarettes. Cell receptors which contain the α subunits are of lower affinity: this is due to their molecular physical configuration. Receptors contacting the β subunits are, conversely, high-affinity, again for similar reasons (Mackowick *et al* 2013). In schizophrenia, the most relevant

receptor type is the α_7 receptor at hippocampal interneurons in area CA 3 (the area designated 3 in the hippocampal Cornu Ammonis). A receptor which contains only α subtypes will therefore have a very low affinity and require a large amount of ligand to activate it. All nicotinic receptor subtypes are ligand-gated ion channels: the ligand is nicotine and the ion is the bivalent calcium Ca^{2+} ion. It is probable that the binding of nicotine to this cholinergic receptor / the passage of ions through it is achieved via a stereochemical molecular change, i.e. allosteric modulation. Certainly, allosteric modulation at the α_7 receptor is one of the pharmacological avenues being explored in the on-going investigations of new pharmacological treatments for schizophrenia (Timmerman *et al* 2007). α_7

receptors operate in correctly-functioning sensory gating, e.g. allowing habituation to repetitive sensory stimuli. In the healthy functional state, trivial stimuli are disregarded. Where sensory gating does not function correctly, these trivial stimuli can acquire inappropriate, even delusional significance because they can no longer be screened out. Delusions can be understood as the conscious interpretation of dysfunctional neurophysiological activity.

At interneurons in the hippocampal CA3 region, sufficient nicotine allows the α_7 receptor to permit influx of calcium into these cells, so depolarising them. These are inhibitory neurones - therefore, sufficient nicotine allows the correct level of inhibition to occur. In this way, repeated sensory stimuli are not sent for further cortical processing, but are disregarded. Similarly, if multiple stimuli are presented, they are prevented from being further developed, i.e. into conscious sensory perception, until the management of the initial stimulus is completed. This is the basis of sensory gating, which can only function correctly if there is a sufficient level of cerebral nicotine. This is usually endogenous, but can be supplemented from external sources, such as tobacco cigarette smoking. As stated above, the α_7 receptor is of low affinity, thus a high level of cerebral nicotine is required. People who suffer from schizophrenia are thus supplementing their deficient endogenous nicotine levels with a high level of tobacco cigarette consumption. Nicotine readily crosses the blood-brain barrier, making cigarette smoking an efficient way of increasing cerebral nicotine levels. Of course, the negative effects to a person's physical health as a result of tobacco cigarette smoking are notorious.

The α_7 nicotinic receptor is a problematic one: as well as having a low affinity for nicotine it desensitises rapidly (Dalack *et al* 1998). This, therefore, is why

nicotine replacement therapy (NRT) with slow-release nicotine patches is unsuitable as an adjunctive treatment for schizophrenia: the hippocampal α_7 receptor would become desensitised and the desired effect - improved sensory gating - is not achieved. A more suitable mode of NRT in schizophrenia is one which replicates the short burst of increased circulating nicotine provided by cigarette smoking. Nicotine chewing-gum or - currently (2017) controversially - the use of an e-cigarette are the two clearest candidates for this.

Excitotoxic cell damage in schizophrenia

At the hippocampus, if cholinergic stimulation is not sufficient, new memory is formed and there is a continual alteration of auto-associative memory. Therefore, in a state of low cholinergic stimulation, the cerebral cortex is bombarded with information which takes on an inappropriate personal significance (Adler *et al* 1998). This constant over-stimulation leads to excitotoxicity (Jarskog 2006) and, eventually, to cerebral tissue loss. Where there is constant depolarization of involved neurones, their cell content eventually becomes depleted. As the involved neurones cannot replace their constituents at a sufficient rate, their cell bodies become redundant. The non-functional neurone is cleared by cerebral microglia. Microglial action is exactly analogous to macrophage activity in the peripheral circulation. This, then, is the basis of cortical tissue loss in chronic schizophrenia. - The cerebral atrophy which used to be seen at post mortem examination of the brains of people suffering from chronic schizophrenia is readily explained by this mechanism. A recent Turkish study (Beyazyüz *et al* 2016) found that there were increased levels of serum markers of apoptosis in people with deficit state schizophrenia: what used to be

pejoratively termed 'burnt-out' schizophrenia. Beyazyüz *et al* investigated apoptosis by measuring serum nucleosome levels. Nucleosomes are sites within a cell where DNA is degraded as part of programmed cell death, apoptosis. Therefore, a higher serum nucleosome level is indicative of increased apoptosis. Beyazyüz *et al* compared serum from people with deficit state schizophrenia and non-deficit state schizophrenia. People with deficit state schizophrenia were found to have significantly increased apoptotic activity, which relates to the marked negative symptoms predominant in this type of schizophrenia. Tissue loss has been found in previous post-mortem studies to be especially apparent in the pre-frontal cortex. Indeed, hypo-frontality is one of the neuropsychiatric features of chronic schizophrenia. Hypo-frontality comprises many of the features evident as negative symptoms of schizophrenia, such as anhedonia, bradykinesia, poverty of movement, speech and thought. These symptoms are indicative of a lack of initiation of action in each of these domains. Loss of cerebral cortex in the frontal lobes is certainly one explanation for negative symptoms in schizophrenia, and perhaps explains why these symptoms can be so difficult to treat. An important view here (Lieberman 1999) is that schizophrenia should be regarded as a neurodegenerative disease because of the serious risk of cerebral tissue loss caused by excitotoxicity. Lieberman believes that the re-designation of schizophrenia as a potential neurodegenerative disease will change the view both of those who suffer with this illness and those who treat it. Perhaps, in the former case, this will aid compliance with therapeutic measures. The aim of treatment with nicotinic receptor modulators can therefore be an attempt to prevent the neurodegenerative changes of schizophrenia. The same could be said of all modes of

antipsychotic treatment used in this illness, but the direct prevention of excitotoxic cell damage via, e.g. allosteric modulation at the α_7 nicotine receptor (Timmerman *et al* 2007) is an especially appropriate understanding of antipsychotic treatment. Therefore, more recent work extends the earlier work of Lieberman and Jarskog: if excitotoxicity can be prevented, there is no progression to the neurodegenerative condition of deficit state schizophrenia.

Recent drug developments

Walling *et al* (2016) report on a Phase 2 drug trial of TC 5619 (bradanicline), an α_7 nicotinic receptor agonist being developed as a new treatment for schizophrenia. This group of workers again refers to the copious available evidence supporting this type of drug development. Following on from the discussion above, outcome measurements included assessment of negative symptoms as one of the outcome measures. Their study was an international, multicentre project: it did not find any benefit when TC 5619 was used in terms of negative symptom profile, functional measures or cognitive measures.

However, it was found that schizophrenic subjects who were also tobacco users showed more beneficial results than non-tobacco users. Walling *et al* hypothesise that this is because this group received a two-fold improvement to their nicotinic transmission. Their explanation is that TC-5619 acts pre-synaptically and they theorise that presynaptic action at $\alpha_4\beta_2$ receptors is pro-cognitive. Their conclusion differs slightly from other workers in this field. The more general consensus is that α_7 nicotinic receptor action is beneficial and pro-cognitive, while $\alpha_4\beta_2$ receptor action has a greater role in reinforcement of action and, potentially, in addiction.

Later stage investigation of other new anti-schizophrenia drugs in development has

found that cognitive-enhancing effects were not consistently seen in people with schizophrenia in Phase 2 trials (Wallace and Bertrand 2013). Newer research molecules, when tested in Phase 1 clinical trials demonstrated the cognitive enhancement expected from the theoretical foundations of this work. Unfortunately, Phase 1 trials of these molecules had to be abandoned due to intolerable cardiovascular side-effects. The exact nature of these were not specified in Wallace and Bertrand's review, but vagal nerve involvement may have been relevant, as implied by de Jonge and Ulloa in 2007.

The α_7 nicotinic receptor and inflammation

Investigation into gastrointestinal pathology in the Netherlands (de Jonge and Ulloa 2007) has revealed the importance of cholinergic reciprocal function in the mediation of inflammation. This group noted that previous workers had found that the inflammation inherent in conditions such as ulcerative colitis worsened when the affected individuals stopped smoking. They further investigated this process and discovered the profound anti-inflammatory effect of nicotine when acting at α_7 nicotinic acetylcholine receptors (α_7 NACHRs). With reference to the central nervous system, it has been found that the α_7 nicotinic receptors on cerebral microglia act as anti-inflammatory mediators. As stated above, microglia are the cerebral cells which are analogous to macrophages in the peripheral circulation and so are therefore operative in processes such as tissue loss via excitotoxicity. Sufficient circulating nicotine down-regulates microglial activity, thus has a direct effect on the apoptotic pathway mentioned earlier. This effect is especially marked in those regions where the α_7 NACHR is expressed in greater numbers, such as in the hippocampus and the cerebral cortex. Therefore, nicotine can be

neuroprotective and ultimately enhance cognitive function (de Jonge and Ulloa 2007).

Clinical implications

Finally, an Italian research group has reported on the use of electronic cigarettes in people with schizophrenia who were smokers and who had been admitted to an in-patient facility. The subjects were followed up for one year, which is a welcome contrast to other studies which stop after the markedly insufficient period of twelve weeks. Caponnetto *et al* found that 50% of their study subjects achieved sustained abstinence from tobacco consumption. They also quantified symptoms in their subjects with the well-known and consistently validated instruments SANS (Scale for the Assessment of Negative Symptoms) and SAPS (Scale for the Assessment of Positive Symptoms). Although they mention that there were no negative findings on either scale measurement, they unfortunately do not elaborate on this data. This is most probably because their focus was on continued tobacco use or otherwise. However, their work undoubtedly demonstrates that e-cigarettes can be used as a physical health-promoting tool for people who do not want to stop smoking such as those with schizophrenic illness. It is worthwhile to extend their work and to investigate whether e-cigarettes can be used as adjunctive agents in symptomatic schizophrenia. As stated above here – as well as by several others – there is a possibility of symptomatic relief in schizophrenia by enhancing hippocampal sensory gating. The other, very beneficial aspect of electronic cigarette use is that the previous smoker's respiratory health is greatly improved by no longer inhaling toxic aromatic hydrocarbons. If that smoker is a person with schizophrenia, then cessation of intake of inhaled toxic aromatic

hydrocarbons means that any antipsychotic medication that they consume will be no longer be so aggressively catabolised by liver enzymes. Thus, there could be a double-edged reason for eventual lower medication requirement: fewer symptoms and reduced hepatic catabolism. People with schizophrenia are known to have an increased incidence of respiratory and cardiovascular disease (Partti *et al* 2015). Quite simply, if they are no longer smoking as many cigarettes, their respiratory health can only be improved as a result (*ibid.*).

As we are at a very early stage in electronic cigarette use, it is the ideal time to further investigate these as potential therapeutic tools. It is also possible at this early stage to regulate the components of e-cigarettes so that potential harmful solvent additives can be excluded from further manufacture. In conclusion, it is useful to recall the difficulties of management of a person who is acutely unwell with schizophrenia. If the overwhelming weight

of evidence leads to the clinical use of electronic cigarettes as an adjunctive measure in the management of schizophrenia, the potential beneficial effects could be considerable. By allowing measures such as use of electronic cigarettes in the in-patient environment, it is quite possible that the number of disruptive incidents on the ward would be decreased. In-patients would therefore be far less affected by the smoking ban present in UK NHS hospitals because they are using a mode of nicotine replacement which could allow them to experience an in-patient stay less negatively than at present. A longer-term consequence may be improved engagement with the therapeutic team and, thus, improved compliance with anti-psychotic medication. A consequence of this latter situation therefore is that the progression to the neurodegenerative deficit state may be avoided by the adoption of this mode of adjunctive treatment: hence there is another potential patient benefit.

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