Revisiting the 'self-medication' hypothesis in light of the new data linking low striatal dopamine to comorbid addictive behavior

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***Abstract*:** Persons with schizophrenia are at a high risk, almost 4.6 times more likely, of having drug abuse problems than persons without psychiatric illness. Among the influential proposals to explain such a high comorbidity rate, the 'self-medication hypothesis' proposed that persons with schizophrenia take to drugs in an effort to cope with the illness and medication side effects. In support of the self-medication hypothesis, data from our earlier clinical study confirmed the strong association between neuroleptic dysphoria and negative subjective responses and comorbid drug abuse. Though dopamine has been consistently suspected as one of the major culprits for the development of neuroleptic dysphoria, it is only recently our neuroimaging studies correlated the emergence of neuroleptic dysphoria to the low level of striatal dopamine functioning. Similarly, more evidence has recently emerged linking low striatal dopamine with the development of vulnerability for drug addictive states in schizophrenia. The convergence of evidence from both the dysphoria and comorbidity research, implicating the role of low striatal dopamine in both conditions, has led us to propose that the person with schizophrenia who develops dysphoria and comorbid addictive disorder is likely to be one and the same.

Keywords: antipsychotics, DSM5, comorbid drug abuse, low striatal dopamine, neuroleptic dysphoria, schizophrenia, subjective negative responses

Introduction

Comorbid substance abuse in schizophrenia has been consistently recognized as high. The epidemiological US catchment area survey in 1990 estimated that 47% of persons with schizophrenia, compared with 13.5% in the general population, has or had evidence of drug abuse [Regier *et al.* 1990]. Patients with schizophrenia are 4.6 times more likely to have drug abuse problems than persons without psychiatric illness [Regier *et al.* 1990]. In essence, over half of those suffering from schizophrenia have a lifetime history of substance abuse disorder. Persons with schizophrenia are more likely to abuse drugs, such as amphetamines, cocaine or cannabis, and, generally, consume large amounts of coffee and smoke heavily [Cuffel, 1992; Dixon *et al.* 1991; Mueser *et al.* 1990; Buckley, 1998; Kavanagh *et al.* 2000]. A number of factors have been identified as underlying the mechanism for such high comorbidity. These include genetic and family vulnerability [Tsuang *et al.* 1998, 2001; Smith *et al.* 2008], issues related to medications and side effects [Duncan, 1974a, 1974b; Khantzian, 1985, 1997; Voruganti *et al.* 1997], as well as a host of economic and psychosocial factors [Mueser *et al.* 1990; Duncan and Petosa, 1994.

The self-medication hypothesis

One of the influential proposals to explain the high comorbidity rate has been the self-medication hypothesis in its two versions: the version advanced by Khantzian in 1985 and modified in 1997 [Khantzian, 1985, 1997]; and the earlier version formulated by Duncan over a number of years [Duncan, 1974a, 1974b, 1975] and Duncan and Gold (1985). According to such a hypothesis, persons with schizophrenia take to drug abuse as a direct consequence of dealing with aspects of their

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illness experience or to alleviate some of the side effects of antipsychotic medications, such as dysphoric responses or extrapyramidal symptoms. Though such a hypothesis gained currency in the late 1980s, its origin goes back to the early psychoanalytic formulations proposed in the 1950s, which postulated that drugs are used as a coping mechanism against psychotic aggressive tendencies [Glover, 1956]. None of these early formulations have gained as wide acceptance as the self-medication hypothesis advanced by Khantzian in 1985 and modified in 1997 [Khantzian, 1985, 1997] and which represented the culmination of a series of psychoanalytically based reports by Khantzian [Khantzian, 1975, 1977] proposing that heroin use can be considered as an attempt to cope.

A rival formulation to the Khantzian self-medication hypothesis was advanced by Duncan and colleagues in a series of reports [Duncan 1974a, 1974b, 1975, 1976; Duncan and Gold, 1983], which has been recently extensively reviewed by Achalu [Achalu, 2002]. In contrast to Khantzian's formulations, the proposal by Duncan and colleagues is behaviorally based and makes a clear distinction between drug use and drug abuse. The notions advanced by the Duncan group were that most of the persons who take illicit substances do not meet the criteria for substance abuse, let alone for drug dependence. In essence, Duncan's model is concerned with describing why a minority of those who take illicit drugs nonmedically lose control over their use and become seriously addicted.

The historical debate based on the major differences between the two models proposed by the Duncan and Khantzian groups was recently rekindled by the changes for addictive disorders in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) that abandoned the distinction between use and abuse in favor of a continuum of symptoms that range from mild to severe [American Psychiatric Association, 2013].

Regardless of the differences between the Khantzian and the Duncan models, the self-medication hypothesis, in itself, proved initially attractive, being clinically intuitive and making practical sense.

In support of the self-medication hypothesis, we proposed that neuroleptic dysphoria is likely the missing link between schizophrenia and substance abuse [Voruganti *et al.* 1997]. Based on our study, which included 223 patients with the confirmed diagnosis of schizophrenia, we reported a strong association between neuroleptic dysphoria and substance abuse (odds ratio 4.08, $chi^2 = 21.8$, $p > 0.0001$). Though it is recognized that association is not a causation, the significant odds ratio led us to propose that neuroleptic-induced dysphoria likely plays a significant role in the development of drug comorbidity in schizophrenia. Other clinical studies followed in support of our original finding [Dalack *et al.* 1998]. However, the self-medication hypothesis was criticized for lack of empirical studies and not being capable of explaining the complexity and the full picture of comorbid substance abuse. Additionally, substance abuse can frequently predate the earliest psychotic symptoms [Sevy *et al.* 2001]. The notion that use of illicit drugs alleviates symptoms or side effects was reported to be not totally consistent, as other studies concluded that the relationship between symptoms of schizophrenia and use of illicit substances does not frequently support the view that illicit substances are used to self-regulate symptoms [Addington and Duchak, 1997].

Overall, the self-medication hypothesis over the past few years has gradually lost a good deal of its attractiveness and influence, being to some extent overshadowed by the accelerated interests in basic neurobiological research. None the less, the hypothesis did not completely disappear, likely as a result of its clinically intuitive formulation. With the advent of neuroimaging in the 1990s, as well as the development of more sophisticated neurobiological techniques, it has become possible for us to finally elucidate the neurobiological basis of neuroleptic dysphoria, as well as to clarify the possible link between the dysphoric state and comorbid drug abuse [Voruganti *et al.* 2001; Voruganti and Awad, 2006]. Such emerging new data have led us to revisit the 'self-medication hypothesis' and also to rethink our previously published data about the reported strong association between both conditions [Voruganti *et al.* 1997].

The new understanding of neuroleptic dysphoria and subjective tolerability to antipsychotics

Soon after the introduction of chlorpromazine in the early 1950s, a number of patients experienced an unpleasant altered subjective state which frequently led to dislike of the medication and

eventually contributed to impaired medication adherence behavior [van Putten *et al.* 1981; Hogan *et al.* 1983; Awad, 1993; Awad and Voruganti, 2005]. Such phenomena received various terminologies in the early literature, being referred to at times as 'behavioral toxicity', 'akinetic depression', 'neuroleptic-induced anhedonia' and 'neuroleptic dysphoria' [Voruganti and Awad, 2004].

With the development and introduction of new measuring tools for subjective responses to medications, including our first reliable and validated instrument, the Drug Attitude Inventory (DAI) [Awad, 1993; Hogan *et al.* 1983], research and clinical interests have expanded. The high discriminative ability to accurately assign clinical samples into dysphoric and nondysphoric groups (overall accuracy rate of 88.7%) has consistently demonstrated the serious consequences of neuroleptic-induced dysphoria, particularly its impact on adherence behavior [Hogan *et al.* 1983]. Though dopamine has always been suspected to have a role in the emergence of dysphoric responses, it was not until the more recent development of neuroimaging techniques that it became possible to identify the neurobiological basis of subjective tolerability to antipsychotics.

In a recent study we have experimentally induced neuroleptic dysphoria, following dopamine depletion using α-methylparatyrosine (AMPT) in a group of medication-free persons with schizophrenia who have consistently experienced dysphoria upon administration of antipsychotic medications [Voruganti *et al.* 2001]. Our dopamine depletion single photon emission computed tomography (SPECT) study proved to be the first to link emerging dysphoria to striatal dopamine binding ratio. Details of the study design, as well as complete results, are outlined in a previous publication [Vorguanti *et al.* 2001]. Additionally, observations over the subsequent 48 hours allowed us to note the cascade of subjective and behavioral events that followed dopamine depletion, which served as the experimental equivalent of dopamine blockade by antipsychotics [Voruganti and Awad, 2006].

Of interest in our study has been the observation of marked individual variability in dopamine receptor binding ratios among the drug-free subjects studied, an observation that is consistent with the earlier report by Seeman and colleagues [Seeman *et al.* 1989]. The severity of dysphoric responses inversely correlated with the incremental changes in D2 receptor binding ratios ($r = -0.82$, $p < 0.01$). Such observations provided for the first time an explanation of why not every patient receiving antipsychotic medications develops neuroleptic dysphoria. Only those patients who have lower dopamine receptor functioning to start with seem to be more vulnerable to the blocking effect of potent dopamine D2 antagonists which, in turn, further impairs striatal dopamine functioning. A number of other neuroimaging studies added more confirmation to our findings in support of the role of low striatal dopamine in the genesis of dysphoric responses [de Haan *et al.* 2006; Mizrahi *et al.* 2009]. Additionally, observing the cascade of events that followed dopamine depletion over the next 48 hours, the earliest behavioral change noted was the altered subjective state, which was experienced just a few hours after ingestion of the medication [Voruganti and Awad, 2006]. Such an experimental finding is consistent with clinical observations of patients experiencing dysphoric response as early as a few hours after ingesting the medication [Awad and Hogan, 1985]. Additionally, our data revealed that the phenomenon of neuroleptic dysphoria is not simply an affective change, but is more complex and includes motor, cognitive and motivational components.

Recent information about the neurobiology of comorbid addictive states

With accelerated basic science research and the advent of sophisticated neuroimaging techniques, new insights into the neurobiology of comorbid addictions were revealed. The developmental neuropathology in the hippocampal and prefrontal cortex pathways has been implicated in the development of the psychotic symptoms, as well as to the vulnerability to addiction behavior *via* dysfunctional interaction with the nucleus accumbens [Chambers *et al.* 2001]. In essence, addictive states can be a primary independent symptom of the schizophrenia disease process itself. Similarly, Volkow and colleagues suggested that substance abuse can arise from an impairment of top–down inhibitory control arising from impairment in the frontal lobe functioning [Volkow *et al.* 2011]. Though the question still remains open, there is good agreement about the likely role of dopamine. Other less investigated neurotransmitters, such as glutamatergic and GABAnergic, have also been implicated in the development of addictive behavior, though their

role is not yet completely clarified [Thoma and Daum, 2013]. Both schizophrenia and comorbid addictive states share a common neuronal circuitry. Additionally, dopamine activities in the nucleus accumbens have been implicated in the mechanism of reinforcement of almost all drugs of abuse [Koob and Le Moal, 1997]. In 2001, we reported probably the first *in vivo* neuroimage of cannabis-induced dopamine release in the striatum [Voruganti *et al.* 2001].

Recent experimental support of the role of striatal dopamine in the genesis of comorbid addictive states was provided by Dalley and colleagues, who demonstrated low striatal D2 dopamine receptor binding as a predisposing factor in cocaine use in rhesus monkeys [Dalley *et al.* 2007]. Reduction in dopamine D2 receptor binding has also been associated with enhanced impulsivity in rats, a mechanism implicated in the genesis of addictive behavior [Everitt *et al.* 2008].

Clinically, striatal dopamine signaling in the limbic striatal region, which has been recently reported to be associated with the success or failure of cocaine treatment with low dopamine transmission, is linked to treatment failure [Martinez *et al.* 2011].

More recently, direct evidence has been provided for significant blunting of dopamine release in all striatal regions in subjects with schizophrenia and drug abuse compared with the increased dopamine release in subjects with schizophrenia without drug abuse [Trifilieff and Martinez, 2014; Thompson *et al.* 2013]. Despite the blunting, dopamine-release was still associated with the amphetamine-induced changes in positive symptoms [Thompson *et al.* 2013]. Such recent data suggest that persons with schizophrenia and comorbid drug abuse suffer from combined dysfunction: increased dopamine sensitivity in the area of the striatum more responsible for psychotic symptoms and the reduced sensitivity to dopamine-release in the striatal region associated with reward and enforcement. The interpretation of such important findings is that such alterations in dopamine release could initiate a vicious circle of using drugs to self-medicate, which in turn can only worsen the psychotic symptoms. Such reported blunting of dopamine release in all striatal regions in persons with schizophrenia and comorbid drug abuse can also explain the reported frequent association of vulnerability to addictive behavior and the development of neuroleptic dysphoria, as we reported earlier [Voruganti *et al.* 1997].

Comorbid substance abuse and neuroleptic dysphoria – connecting the dots

It is already recognized that low striatal dopamine functioning is implicated in the development of both dysphoric responses to antipsychotic medications as also underlie the development of vulnerability for comorbid addictive states. Taken together, such new data add a neurobiological support to conclusions from our previous study [Voruganti *et al.* 1997], proposing a possible link between both conditions. It is plausible, then, that the person who is vulnerable to develop dysphoria may be one and the same who also can present with vulnerability for an addictive state. Such new synthesis not only revives, but also confirms a neurobiological basis for the self-medication hypothesis, particularly the version proposed by Duncan [Duncan, 1974a, 1974b].

Such new information also has implications for the choice of the antipsychotic medication used for treatment of psychosis with comorbid drug abuse. The preference for choosing an antipsychotic in such a situation needs to be based on the pharmacological properties of medications, selecting an antipsychotic which has low potency for dopamine D2 antagonism or an antipsychotics that does not stay long on the dopamine receptor, so as not to further impair striatal dopamine functioning [Samaha, 2014; Awad, 2012]. Chronic dopamine blockade can lead to postsynaptic upregulation, which in turn enhances the reinforcement properties of drugs of abuse. Such new information can explain the reported beneficial effects of medications such as clozapine [Green *et al.* 2008] or other new atypical antipsychotics, such as olanzapine [Littrell *et al.* 2001] and rispiridone [Smelson *et al.* 2002]. Aripiprazole being an agonist/antagonist is expected theoretically to be a useful antipsychotic in such situations; however, results from the ongoing clinical trials are not yet available.

Our proposed hypothesis can also provide an explanation of why not every person using drugs ends up being addicted, losing control over drug use, as initially suggested by the Duncan group's version of the self-medication hypothesis [Duncan, 1974a, 1974b, 1975]. In essence, the effect of the dynamic interaction between the striatal dopamine state and the pharmacological dopamine-blocking

properties of the particular antipsychotic determines the outcome, and whether the person experiences a dysphoric reaction and develops a vulnerability to an addictive state. In other words, those persons who develop an addictive state are neurobiologically different and constitute a subgroup characterized by low striatal dopamine functioning.

Our proposed neurobiological link between neuroleptic dysphoric reactions and the vulnerability to develop addictive states can prove clinically useful. Since dysphoric reactions and negative subjective responses appear early in the cascade of events that take place after ingestion of the antipsychotic, it can also serve as an early clinical marker for the person who is potentially likely to develop a vulnerability to drug abuse [Voruganti and Awad, 2006].

As persons with schizophrenia and comorbid drug abuse require treatment with an antipsychotic, the question we raised in a previous article is whether it is time to consider comorbid addictive states as an indication for antipsychotic drug development [Awad, 2012]. So far, all clinical trials conducted in the process of development of new antipsychotics have considered comorbid substance abuse as an exclusion criterion. The recent new data linking low striatal dopamine to the development of both dysphoric subjective reactions and vulnerability for comorbid addictive states, as well as the evolving notion that addictive states may be related to the schizophrenia process itself, taken all together adds to the importance and urgency for having a further look at how the development of new antipsychotics should proceed. Furthermore, it highlights the urgent need for more focused clinical studies capitalizing on information generated by the accelerated research in basic sciences. The recent interest in the development of large computerized and integrated mental health databases can provide not only larger, but also potentially more heterogeneous, populations that can allow for opportunities to explore in-depth 'signals' uncovered in single studies.

Research and public health interests about the negative impact of comorbid drug abuse in schizophrenia on clinical outcomes need to be enhanced. Drug comorbidity in schizophrenia can lead to significant personal and family sufferings as a result of the frequent relapses that require numerous hospitalizations and, as such, lead to increased medical resources utilization, adding to the already high cost of psychiatric care.

Conclusion

Based on recent data demonstrating the role of low striatal dopamine in the genesis of neuroleptic-induced dysphoria as well as comorbid vulnerability for addictive states, we propose that the person with schizophrenia experiencing negative subjective and dysphoric responses can be one and the same who develops vulnerability to comorbid addictive states. Such a new formulation not only adds basic clarification about the link between both conditions, but provides neurobiological support of the 'self-medication hypothesis'. As subjective and dysphoric neuroleptic responses are the earliest experiences following ingestion of the antipsychotic medication, it is possible that such subjective negative responses can serve as an early clinical marker for potential development of vulnerability to addictive states. Similarly, it underscores the importance of choosing an antipsychotic appropriate to such clinical situations (i.e. an antipsychotic which is not a strong dopamine D2 blocker) in order to not further compromise dopamine striatal functioning. Such a new understanding also clarifies why not many patients with schizophrenia and comorbid drug abuse treated with the potent dopamine D2 blockers, such as haloperidol, have been rarely able to exert adequate control over their addictive behavior. It also highlights the urgent need to re-examine the process of development of new antipsychotics by establishing comorbid substance abuse in schizophrenia as possibly a new indication for medication development.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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