Is Neuroleptic Dysphoria a Variant of Drug-Induced Extrapyramidal Side Effects?

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Objectives: Neuroleptic drugs induce psychological side effects such as dysphoria, cognitive impairment, and loss of motivation. These side effects were largely underrecognized and trivialized in the past as variants of extrapyramidal side effects (EPSEs). We review the recent literature on the subject and clarify the relation between neuroleptic-induced dysphoria and EPSEs.

Methods: We critically examined clinical, interventional, neuroimaging, and basic science studies published in the past 10 years, delineating the temporal, phenomenological, biochemical, and neuroanatomical relation between dysphoria and EPSEs.

Results: Subjective responses occur within 4 to 6 hours of neuroleptic use, whereas acute dystonia is often observed within 24 hours and parkinsonian syndrome after 5 to 7 days. Neuroleptic-induced dopaminergic blockade mediates both dysphoria and EPSEs. However, impaired dopamine function in the nucleus accumbens seems to give rise to dysphoria, whereas blockade of D_2 receptors in the nigrostriatal system is responsible for EPSEs.

Conclusion: The earlier notion that neuroleptic dysphoria is a variant of EPSEs was simplistic and speculative. Exploring the differences rather than dwelling on the similarities will likely enhance our understanding of dopamine's role in the origin of varied side effects and in their distinctive characteristics.

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Clinical Implications

- Clinical monitoring of the side effects of antipsychotic drugs should include specific inquiry into aspects of subjective tolerability.
- If unchecked, poor subjective tolerability may lead to nonadherence to prescribed treatment, clinical instability, and other adverse consequences.
- Exploring the nature of both spontaneous and iatrogenic dysphoria outside the context of schizophrenia and neuroleptic therapy will broaden our understanding and appreciation of its implications.

Limitations

- Studies of neuroleptic dysphoria in particular and subjective responses to medications in general have been few and far between.
- In vivo studies involving neurochemistry of the brain are hampered by technical limitations, which prevents the drawing of firm associations between clinical events and neurobiological correlates.
- Little has been known about the nature of dysphoria occurring in clinical situations apart from neuroleptic therapy.

Key Words: *neuroleptics, dysphoria, extrapyramidal side effects, dopamine*

The introduction of chlorpromazine in the 1950s was quickly followed by a series of reports on its adverse effects (1). Over the next 2 decades, extensive worldwide use of neuroleptics led to a compendium of systemic, neurological, and psychological adverse effects. During this period, considerable controversy and confusion existed with regard to naming and classifiying adverse events, especially the subtle and underrecognized subjective effects such as dysphoria, cognitive deficits, and loss of motivation resulting from neuroleptic use. The "lumpers" included them among extrapyramidal side effects (EPSEs), since drug-induced parkinsonian syndrome was already well recognized, systematically studied, and better understood at the time (2). Consequently, all the other neurological and psychological side effects whose nature and mechanisms were not clearly understood came to be included in the category of EPSEs. The "splitters" preferred to categorize them as psychic, behavioural, or mental side effects solely to distinguish them from somatic and neurological side effects (3). The nature of these subjective adverse effects and their clinical implications were carefully studied by some researchers, whereas the subjective nature of these responses created a sense of uncertainty and disinterest among many others. This article examines the original notion that neuroleptic dysphoria is a variant of EPSEs and considers recent findings that could help to redefine the relation between neuroleptic-induced dysphoria and EPSEs.

Background

Neuroleptic dysphoria refers to the unpleasant subjective responses reported during neuroleptic therapy. Patients' descriptions often include terms such as "feeling blah, listless, tired, and lacking interest and ambition." Dysphoric feelings have been reported to occur within a few hours of administering the first dose of neuroleptic medications and seem to persist over the following weeks and months, leading to several important clinical consequences (4–8). Immediate clinical manifestations include complaints of subjective intolerance, reluctance to take antipsychotic drugs, and even outright treatment refusal (9). Failure to address these problems may lead to long-term consequences such as nonadherence to treatment, clinical instability characterized by relapses and rehospitalizations, suicidal behaviour, comorbid substance abuse, and compromised quality of life (7,10–15).

In the 1970s, neuroleptic dysphoria was considered by some to be a form of an affective syndrome, while others included it in the cluster of extrapyramidal syndromes (for example, akinesia, dystonia, and akathisia). The notion that dysphoric responses were a variant of EPSEs was supported by clinical observations: both phenomena occurred during the first week of neuroleptic therapy, they were often induced by high-potency neuroleptics, and their severity seemed to be related to the degree of dopaminergic blockade. It was also noted by others that dysphoria and EPSEs did not always coincide. EPSEs were relieved by antiparkinsonian drugs, whereas dysphoria was not, and dysphoric responses were noted much earlier than EPSEs during the course of neuroleptic therapy. By the 1980s, it became obvious that clinical observations alone were not adequate to resolve the issue of defining and classifying the status of neuroleptic dysphoria.

Recent Research

Because dysphoria is subjective, it seemed difficult to study the phenomenon using modern scientific principles and rigour. The enthusiasm for studying dysphoria subsided by the 1980s and research stagnated. In the 1990s, 3 significant developments helped to rejuvenate interest in dysphoria, especially interest in exploring its neurobiological underpinnings. These developments were the popularity of clinical experiments involving chemical probes, progress in the area of neuroimaging, and the introduction of second-generation antipsychotic drugs.

Experimental Studies Involving Chemical Probes

Research into studying the role of dopamine took a major leap with the use of alpha-methyl paratyrosine (AMPT) as a chemical probe to manipulate neurotransmitter dynamics in the brain. The technique was perfected by Laruelle and colleagues, primarily for in vivo studies aimed at studying dopamine function in schizophrenia (16). The experimental protocol involved administering AMPT for 48 hours to induce a dramatic, but temporary and reversible, depletion of dopamine and studying consequent changes in receptor occupancy. Clinical rating scales administered during the experiment included a visual analogue scale to measure changes in emotional status. Results indicated significant changes in anxiety, depression, and extrapyramidal symptoms ensuing from the AMPT-induced dopamine depletion. These findings, along with the other biological indices of dopamine depletion (homovanillic acid and D_2 receptor occupancy), resurrected the putative link between impaired dopamine function and dysphoric subjective responses.

Recently, we reported data from a comprehensive study of the phenomenology of dysphoria, including its relation to other extrapyramidal symptoms and striatal dopamine D_2 binding ratio, which was carried out using the same experimental AMPT paradigm (17). In this focused investigation, subjective responses to AMPT ingestion were systematically monitored and documented through serial administration of the Addiction Research Center Inventory (18), the Drug Attitude Inventory (19,20), and the Profile of Mood States (POMS)

(21). Subjective (dysphoric) responses were the earliest to be captured by the rating scales, followed by the emergence of akathisia and parkinsonian symptoms, respectively. Perceived psychomotor slowing, lack of pleasure, and preference to remain isolated were reported within 6 hours of receiving AMPT; akathisia was noted after 24 to 36 hours; rigidity and tremor became evident toward the end of 48 hours.

These observations were again substantiated by Verhoeff and colleagues (22), who noticed distinctive shifts in various POMS subscales that suggested emergence of dysphoria during AMPT-induced dopamine depletion.

The AMPT studies consistently demonstrated that rapid depletion of dopamine brings about a range of profound systemic, neurological, psychological, cognitive, and affective changes, the latter being in the form of dysphoria. In particular, our study indicated that the time of onset of these changes follows a distinctive pattern. This differential onset of the manifestations of impaired dopamine function is also consistent with the onset of side effects during the course of neuroleptic treatment.

Clinical Observations

Cross-sectional as well as long-term follow-up switch studies in schizophrenia indicate better subjective tolerability and less-frequent dysphoria on second-generation, compared with first-generation, antipsychotics (23–25). The topic is reviewed in greater detail in this issue (26).

Why are the novel antipsychotic drugs tolerated better, compared with the neuroleptics? A review of the concept of atypicality and the proposed mechanisms of action of second-generation antipsychotic drugs may provide some clues toward their low dysphoria liability and improved tolerability. The "dopaminergic" theories of atypicality are based on the following themes: the extent of dopamine D_2 receptor blockade (27,28); the degree of affinity of drug molecules to D_2 receptors (29,30); the contribution of other dopamine receptors, such as D_1, D_3, and D_4, toward subjective attributes such as sensation-seeking behaviour (31); prefrontal dopamine release, either through serotonergic action or independently (32); and selective dopaminergic blockade in the shell of the nucleus accumbens that does not affect the core (33). The original speculation was that the ratio of D_2 and 5-HT_2 receptor blockade is crucial in determining EPSE liability or the lack of it (28,34).

Advances in neuroimaging made it feasible to explore the neurochemical basis of subjective responses, especially the pivotal role of dopamine. We include here a summary of the seminal studies (for a detailed review, see de Haan and colleagues; 35).

Neuroimaging Data

Employing various experimental techniques, several receptor-imaging studies in the recent past have attempted to address the relation between altered dopaminergic function and disturbed mood in schizophrenia. Fujita and colleagues used a protocol consisting of AMPT administration and single photon emission computed tomography (SPECT) imaging with [^{123}I]epidepride in healthy volunteers and were able to demonstrate an association between increased D_2 binding potential in the temporal cortex and a corresponding worsening of dysphoric mood (36). Hietala and others examined the striatal dopamine levels of 10 drug-naïve, first-episode schizophrenia patients with [^{18}F]-6-L-fluorodopa ([^{18}F]DOPA) positron emission tomography (PET) imaging and found a strong correlation (r = 0.86 to 0.9) between low striatal dopamine and scores on the depressive items on the Positive and Negative Symptom Scales (37).

De Haan and colleagues used [^{123}I]iodobenzamide ([^{123}I]IBZM) SPECT imaging to estimate striatal D_2 occupancy rates in schizophrenia patients treated with olanzapine or risperidone and found a significant correlation between the percentage of D_2 occupancy and dysphoric responses (38). In another recent study, a group of drug-free schizophrenia patients (n = 13) were administered AMPT (4 to 5 g daily) over a 48-hour period, and the progressive changes in their mental status were measured with standardized rating scales at 12-hourly intervals. Changes in their striatal D_2 receptor occupancy were simultaneously quantified with [^{123}I]IBZM SPECT imaging (17). The severity of dysphoric responses correlated inversely with the incremental changes in D_2 receptor binding ratios (r = –0.82, $P < 0.01$).

Neuroanatomical Studies

Cumulative knowledge acquired from anatomical and histological studies in rodents and primates has further enhanced our ability to decipher the neural substrates of neuroleptic effects. Intracranial electrical stimulation, chemical lesioning studies with 6-hydroxy dopamine, histochemistry, autoradiography, and immunoreactivity techniques have not only facilitated mapping of dopamine projections but have also identified meaningful anatomical-functional links. Of all the different projections described, perhaps the ones most relevant to the present discussion are the nigrostriatal and mesoaccumbens projections. Dopaminergic blockade in the nigrostriatal system is responsible for the occurrence of parkinsonian syndrome, whereas the same impairment in the accumbens complex seems to give rise to dysphoric responses.

The nucleus accumbens is a part of the basal forebrain and is closely linked to the ventral striatum and extended amygdala, both anatomically and functionally. Recent

anatomical studies have shown that the accumbens has 2 vaguely defined anatomical components—a central core and a peripheral shell—that have histological and functional specificity (39). The nucleus accumbens has been identified as a critical component of the brain's reward system and is significantly implicated in determining motivational behaviour and its disorders, such as drug abuse. Drugs of abuse, including cocaine, amphetamines, and morphine, preferentially stimulate the release of dopamine and increase the energy metabolism in the shell of the nucleus accumbens. Recent neurotensin and Fos immunoreactivity studies have also demonstrated that neuroleptics seem to exert their actions on the core as well as on the shell, while the new atypical antipsychotic drugs have a preferential effect on the dorsomedial aspects of the shell (32,33).

New Insights

A review of recent developments (40) suggests 2 predominant themes: 1) provocation studies involving AMPT and neuroimaging studies confirm that dopaminergic blockade is responsible for both dysphoria and extrapyramidal syndromes; 2) clinical and neuroanatomical studies are, however, able to distinguish between dysphoria and EPSEs in terms of their neural substrates and time of onset. These observations neither clearly support nor refute the notion under discussion, but they have helped to redefine the relation between dysphoria and EPSEs with an improved level of scientific sophistication.

The Oxford English Dictionary defines variant as "a form or version of something differing in some respect from other forms of the same thing" (41). The notion that neuroleptic-induced dysphoria is a variant of EPSEs carries a connotation that EPSEs are a well-defined core phenomenon, whereas dysphoria is an alternative presentation of the same entity. As afflictions of the motor system, akinesia, rigidity, tremor, and dystonia share common characteristics and may be considered variants of neuroleptic-induced extrapyramidal syndrome. Conversely, neuroleptic dysphoria is primarily characterized as a subjective or psychological response, albeit caused by the same pathophysiology, that is, impaired dopamine function. Based on the review of recent literature, it would be more appropriate to consider both dysphoria and EPSEs as variants or manifestations of drug-induced dopaminergic blockade.

Implications

How relevant is it to ask whether or not dysphoria is a variant of neuroleptic-induced EPSEs? With the arrival of the second-generation antipsychotic drugs, neuroleptic-induced dysphoria and EPSEs are becoming less frequent, giving the false impression that this discussion has become somewhat academic. However, academic pursuits have heuristic value, and the study of neuroleptic dysphoria has implications for new drug development and for understanding the pathophysiology of a spectrum of dysphoric states, including substance abuse. Subjective tolerability is recognized as a desirable characteristic of an ideal antipsychotic drug, setting a new standard for the development of antipsychotic compounds. Also, recognition of the nucleus accumbens as the putative neural substrate for both dysphoria and substance abuse provides scope for understanding the neurobiological underpinnings of schizophrenia–substance abuse comorbidity.

References

1. Hollister LE. Complications from the use of tranquilizing drugs. N Engl J Med 1957;257:170–7.
2. Barnes TRE, Braude WM. Akathisia variants and tardive dyskinesia. Arch Gen Psychiatry 1985;42:874–8.
3. Di Mascio A, Shader RL. Behavioural toxicity. In: Di Mascio A, Shader RL, editors. Psychotropic drug side effects: clinical and theoretical perspectives. Philadelphia (PA): Williams and Wilkins; 1972. p 116–23.
4. Serafetinides EA, Clark ML. Psychological effects of a single dose antipsychotic medication. Biol Psychiatry 1973;7:263–7.
5. Awad AG. Subjective response to neuroleptics in schizophrenia. Schizophr Bull 1993;19:609–18.
6. Awad AG, Hogan TP. Early treatment events and prediction of response to neuroleptics in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 1985;9:585–8.
7. Awad AG, Hogan TP, Voruganti LNP, Heslegrave RJ. Patients' subjective experiences on antipsychotic medications: implications for outcome and quality of life. Int Clin Psychopharmacol 1995;10(Suppl 3):123–33.
8. Sachdev P. Neuroleptic dysphoria In: Akathisia and restlessness. London: Cambridge University Press; 1995. p 42–7.
9. Van Putten T, Mutalpassi LR, Malkin MD. Phenothiazine-induced decompensation. Arch Gen Psychiatry 1974;30:102–5.
10. Diamond R. Drugs and quality of life: the patient's point of view. J Clin Psychiatry 1985;46:29–35
11. D'Mello DA, Boltz MK, Msibi B. The relationship between concurrent substance abuse in psychiatric patients and neuroleptic dose. Am J Drug Alcohol Abuse 1995;21:257–65.
12. Blyler CR, Fenton WS. Satisfaction with treatment outcome and non-compliance in schizophrenia. Schizophr Res 1997;24:205.
13. Voruganti L, Heslegrave RJ, Awad AG. Neuroleptic dysphoria may be the missing link between substance abuse and schizophrenia. J Nerv Ment Disord 1997;185:463–5.
14. Buckley P. Substance abuse in schizophrenia: a review. J Clin Psychiatry 1998;59(Suppl 3):6–30.
15. Awad AG. Behavioural and subjective side effects. In: Kane JM, editor. Managing the side effects of drug therapy in schizophrenia. London: Science Press; 1999. p 1–14.
16. Laruelle M, D'Souza CD, Baldwin RM, Abi-Dargham A. Imaging D_2 receptor occupancy by endogenous dopamine in humans. Neuropsychopharmacology 1997;17:162–74.
17. Voruganti L, Slomka P, Zabel P, Costa G, So A, Mattar A, and others. Subjective effects of AMPT-induced dopamine depletion in schizophrenia: the correlation between D_2 binding ratio and dysphoric responses. Neuropsychopharmacology 2001;25:642–50.
18. Haertzen CA. Addiction Research Centre Inventory (ARCI) development of a general drug estimation scale. J Nerv Ment Disord 1965;141:300–7.
19. Hogan TP, Awad AG, Eastwood RC. A self-report scale predictive of drug compliance in schizophrenia: reliability and discriminate ability. Psychol Med 1983;13:177–83.
20. Awad AG, Voruganti LNP, Heslgrave RJ. Assessment of the patient's subjective experiences in acute neuroleptic treatment implications for compliance and outcome. Int Clin Pyschopharmacol 1996;11(Suppl 2):55–60.
21. McNair DM, Lorr M, Droppleman L. Manual for the Profile of Mood States. San Diego (CA): Educational and Industrial Testing Services; 1992.
22. Verhoeff NP, Christensen BK, Hussey D, Lee M, Papatheodorou G, Kapur S. Effects of catecholamine depletion on D_2 receptors binding motivation and attentiveness in humans: a replication study. Pharmacol Biochem Behav 2003;74:425–32.

23. Voruganti LNP, Cortese L, Ouyewumi L, Kotteda V, Zirul S, Awad AG. Comparative evaluation of conventional and new antipsychotic drugs: a follow-up study. Schizophr Res 2000;43:135–45.
24. Voruganti L, Cortese L, Ouyewumi L, Cernovsky J, Zirul S, Awad AG. Switching from conventional to novel antipsychotic drugs: results of a prospective naturalistic study. Schizophr Res 2002;57:201–8.
25. Awad AG. Antipsychotic medications: compliance and attitudes toward treatment. Curr Opin Psychiatry. Forthcoming.
26. Awad AG, Voruganti LNP. New antipsychotics, compliance, quality of life and subjective tolerability: are patients better off? Can J Psychiatry 2004;49:297–302.
27. Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D_2 dopamine receptor binding in the living human brain by PET. Science 1986; 231:258–61.
28. Kapur S, Zipursky RB, Jones C, Remington G, Houle S. Relationship between dopamine D_2 occupancy, clinical response, and side-effects: a double-blind PET study of first episode schizophrenia. Am J Psychiatry 2000;157:514–20.
29. Seeman P, Tallerico T. Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D_2 receptors yet occupy high levels of these receptors. Mol Psychiatry 1998;3:123–34.
30. Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? A new hypothesis. Am J Psychiatry 2001;158:360–9.
31. Ekelund J, Lichterman D, Jarvelin MR, Peltonen L. Association between novelty seeking and the type 4 dopamine receptor gene in 9 large Finnish cohort samples. Am J Psychiatry 1999;156:1435–55.
32. Kuroki T, Metzer HY, Ichikawa J. Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. J Pharmacol Exp Therap 1999;288:774–81.
33. Taber MT, Das S, Fibiger HC. Cortical regulation of subcortical dopamine release: medication via the ventral tegmental area. J Neurochem 1995;65:1407–10.
34. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT_2 and D_2 receptor occupancy of clozapine, risperidone and olanzapine in schizophrenia. Am J Psychiatry 1999;156:286–93.
35. de Haan L, Lavalaye J, Van Bruggen M, Van Nimwegen L, Booij J. Subjective experience and dopamine D_2 receptor occupancy in patients treated with antipsychotics: clinical implications. Can J Psychiatry 2004;49:290–6.
36. Fujita M, Verhoeff, Varrone A, Zoghbi S, Baldwin RM, Jatlow PA, and others. Imaging extrastraital dopamine D(2) receptor occupancy by endogenous dopamine in healthy humans. Eur J Pharmacol 2000;387:179–88.
37. Hietala J, Syvalahsi E, Vilkman H, Vuorio K, Rakkolainen V, Bergman J, and others. Depressive symptoms and presynaptic dopamine functions in neuroleptic naïve schizophrenia. Schizophr Res 1999;35:41–50.
38. de Haan L, Lavalaye J, Linszen D, Dingemans PMAJ, Booij J. Subjective experience and striatal dopamine D_2 receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. Am J Psychiatry 2000;157:1019–20.
39. Heimer L, Alheid G, de Olmos JS, Groenewegen HJ, Haber SN, Harlan R, and others. The accumbens: beyond the core shell dichotomy. In: Sallaway SP, Malloy PF, Cummings JL, editors. The neuropsychiatry of limbic and subcortical disorders. Washington (DC): American Psychiatric Press; 1997.
40. Voruganti LP, Awad AG. Neuroleptic dysphoria: toward a new synthesis. Psychopharmacology 2004;171:121–31.
41. The Oxford English Dictionary. 2nd ed. Oxford (UK): Clarendon Press; 1989.

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Résumé : La dysphorie neuroleptique est-elle une variante des effets secondaires extrapyramidaux d'origine médicamenteuse?

Objectifs : Les médicaments neuroleptiques provoquent des effets secondaires psychologiques comme la dysphorie, la déficience intellectuelle et la perte de motivation. Ces effets secondaires ont été largement sous-reconnus et banalisés par le passé comme étant des variantes des effets secondaires extrapyramidaux (ESEP). Nous examinons la documentation récente sur le sujet et clarifions la relation entre la dysphorie induite par les neuroleptiques et les ESEP.

Méthodes : Nous avons fait un examen critique des études cliniques, d'imagerie interventionnelle et de science fondamentale publiées dans les 10 dernières années, délimitant la relation temporelle, phénoménologique, biochimique et neuro-anatomique entre la dysphorie et les ESEP.

Résultats : Des réactions subjectives se produisent dans les 4 à 6 heures suivant l'utilisation d'un neuroleptique, tandis qu'une dystonie aiguë est souvent observée dans les 24 heures, et le syndrome parkinsonien, après 5 à 7 jours. Le blocage de la dopamine induit par neuroleptique facilite la dysphorie et les ESEP. Toutefois, une fonction déficiente de la dopamine dans le noyau accumbens semble occasionner la dysphorie, tandis que le blocage des récepteurs D_2 dans le système nigro-strié est responsable des ESEP.

Conclusion : La notion passée selon laquelle la dysphorie neuroleptique est une variante des ESEP était simpliste et spéculative. Rechercher les différences plutôt qu'insister sur les similitudes peut probablement accroître notre compréhension du rôle de la dopamine dans l'origine des effets secondaires variés et dans leurs caractéristiques distinctes.