JANUARY 20

Evidence of Neuroleptic Drug-Induced Brain Damage

HAZARDS, PSYCH DRUGS

Patients:
A partial, Annotated Bibliography
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Although patients, families and the public were not informed – some would argue they were deceived – clinical psychiatrists and researchers have long known about severe adverse drug reactions (ADR) and disabling changes in the central nervous system in a high percentage of patients taking standard neuroleptic drugs. Foremost among these is “tardive dyskinesia” (TD), an often irreversible, disfiguring disorder of the central nervous system resulting in a variety of involuntary movements, particularly of the tongue, lips, and jaw. muscle movements which affects 40% to 60% of patients taking neuroleptics. Recent research findings corroborate earlier reports (since 1970) linking TD to a deterioration of cognitive functions (see below).

Other severe ADRs include: “extrapyramidal symptoms” (EPS), Parkinson-like, impaired motor coordination; sedation; extreme restlessness (“akathesia”); reduced cognitive function;as well as cardiovascular effects, orthostatic hypotension, abnormal liver changes, anticholinergic side effects, sexual dysfunction, and weight gain. Psychotic relapse has been linked to long-term neuroleptic treatment –referred to as, “supersensitivity psychosis.” Additionally, there is a one percent risk of “neuroleptic malignant syndrome” (NMS), a potentially fatal side effect. These, and a host of other adverse side effects, cause

most schiz[illegible]ia patients to stop taking these drugs.

In an articl[illegible]en in 1986, Tardive Dyskinesia: Barriers to the Professional Recognitio[illegible]:rogenic Disease, [Journal of Health and Social Behavior,1986, 27: 116-13[illegible]own and Funk stated: "tardive dyskinesia (TD), once regarded by psychiatris[illegible] rare syndrome, is currently recognized as the second most pervasive s[illegible]fect following sedation of antipsychotic drugs." Although evidence li[illegible]TD to neuroleptic drugs had been shown since 1957, Brown and Funk point out that the recognition of TD as a side effect had been "a slow and uneven process, involving psychiatric resistance....Even when physicians believe that patients should be informed about the risks of TD, usually only incomplete information is given, not all patients at risk are informed...." And, they noted, "psychiatrists who are critical of the profession's lax treatment of the problem argue that if doctors were really concerned, they would reduce their use of neuroleptics and reduce dosages when drugs are employed..." and they would fully disclose the risks of TD to their patients.

But a review of the history of TD demonstrates clearly that despite the evidence physicians' disclosure and practice with respect to neuroleptic drugs has remained unchanged, and TD afflicts ever more patients, especially after long-term exposure-estimates range between 40% to 60%. The APA has opposed written informed consent from patients.

Van Putten T, Marder SR (1987) Behavioral toxicity of antipsychotic drugs. J Clin Psychiatry 1987 Sep;48 Suppl:13-9

Extrapyramidal symptoms cause much misery, often go undiagnosed, and can interfere with treatment and rehabilitation. Akinesia is a behavioral state of diminished motoric and psychic spontaneity that is difficult to distinguish from the negative symptoms of schizophrenia. The most useful clinical correlates of akinesia are a subjective sense of sedation and excessive sleeping. Akinesia

interferes w cial adjustment and may manifest as “postpsychotic depression subjective restlessness of akathisia is usually accompanied by telltale foot ments: rocking from foot to foot while standing or walking on the spot. Akath strongly associated with depression and dysphoric responses to neuroleptic has even been linked to suicidal and homicidal behavior in extreme ca

Recent F gs Corroborate high incidence of drug-induced movement disorders:

Miller LG, Jankovic J (1990) Neurologic approach to drug-induced movement disorders: a study of 125 patients.South Med J 1990 May;83(5):525-32. Department of Family Medicine, Baylor College of Medicine, Houston, Tex.

Of 125 patients with neuroleptic (dopamine blocking) drug-induced movement disorders who had been referred to a specialized clinic to differentiate the predominant movement disorder, 63% had tardive dyskinesia, 30% had parkinsonism, 24% had dystonia, 7% had akathisia, and 2% had isolated tremor. Two or more movement disorders coexisted in 31 patients (25%).

Functional disability was more severe in patients with akathisia than in other patients. Women outnumbered men at a ratio of 4:1, except for tardive dystonia which affected both sexes equally. The average at onset was 56 years (range, 13 to 87); 69 patients (55%) had onset of movement disorder in the sixth decade. While tardive dystonia was distributed relatively evenly in all age groups, almost a third of patients with parkinsonism had it in the eighth decade. Haloperidol was implicated in 47 patients (37%), followed by amitriptyline/perphenazine in 30%, thioridazine in 27%, and chlorpromazine in 20%. Metoclopramide-induced movement disorders were found in 10 (8%). Most patients (101 or 81%) had history of psychiatric illnesses, but of these only 44 had psychosis.

Neuroleptic drugs had been prescribed for 33 patients (26%) who had

gastrointes roblems. It is important to recognize and differentiate various drug-induc vement disorders because such differentiation has pathophys and therapeutic implications. Many patients could have been treated wit potent drugs.

Muscettola rbato G, Pampallona S, Casiello M, Bollini P (1999) Extrapyran yndromes in neuroleptic-treated patients: prevalence, risk factors, an ciation with tardive dyskinesia. J Clin Psychopharmacol 1999 Jun;19(3):203-8

ABSTRACT: Prevalence and risk factors for extrapyramidal syndromes (EPS) were investigated in a sample of 1,559 patients. The overall prevalence of EPS was 29.4% (N = 458). Among the EPS-diagnosed patients, Parkinsonism as assessed by the presence of core Parkinsonian symptoms (rigidity, tremor, bradykinesia) was present in 65.9% of patients (N = 302), akathisia in 31.8% (N = 145), and acute dystonia in 2.1% (N = 10).

EPS was diagnosed in 50.2% of 285 patients with persistent tardive dyskinesia (TD). Distribution of EPS in patients with TD showed that tremor and akathisia were more frequent in peripheral TD cases than in orofacial TD cases. Furthermore, there was a stronger association of NL-induced parkinsonism with peripheral TD than with orofacial TD. This study suggests that the association between EPS and TD may be limited to specific subtypes of TD. Peripheral TD showed a higher association with parkinsonism and with akathisia, suggesting that these symptoms may share a common pathophysiology.

Bristow MF ... :h SR (1993) Pitfalls and problems of the long term use of neuroleptic ... in schizophrenia. Drug Safety 1993 Feb;8(2):136-48. Academic Departmer ... sychiatry, Charing Cross and Westminster Medical School, London, Er ...

ABSTRAC ... ough acute and immediate extrapyramidal syndromes are common a ... he case of neuroleptic malignant syndrome, may have serious sequelae, t ... st important problem with psychotropic medication in schizophrenia remains the tardive movement disorders. These are increasingly recognised as being aetiologically as well as symptomatically heterogeneous. Although risk factors are being identified with greater clarity, there is little in the way of effective treatment. This suggests that clinicians must embark on long term neuroleptic treatment with vigilance. Clozapine alone has few extrapyramidal effects, and has been described in isolated instances as improving established movement disorders. However, haematological idiosyncrasies will preclude its use in all where compliance is uncertain. Its superior efficacy will hopefully give impetus to research into safer analogues.

Hansen TE, Brown WL, Weigel RM, Casey DE (1992) Underrecognition of tardive dyskinesia and drug-induced parkinsonism by psychiatric residents. Gen Hosp Psychiatry 1992 Sept; 14(5):340-4. Portland Veterans Affairs Medical Center, Oregon Health Sciences University 97207.

Recognition of tardive dyskinesia (TD) and other neuroleptic, drug-induced, extrapyramidal side effects presents a major challenge in modern clinical psychopharmacology. Failure to recognize these disorders can lead to poor patient care and may contribute to societal pressure for external control of psychiatric practice. This study reports the occurrence of tardive dyskinesia and drug-induced parkinsonism (DIP) in 101 inpatients, and documents under recognition of both disorders by resident physicians.

Researche d TD in 28% of cases and residents only described TD (or symptoms in 12%. The researcher determined DIP prevalence rate of 26% contrasted in 11% rate found by residents. Patients with psychotic disorders were more than other patients to have researcher-identified TD, whereas DIP (resea ases) occurred more often in patients with affective diagnoses. Residents t to miss milder cases of TD, and to miss DIP in younger patients and in pati ith affective disorders. Improved teaching and clinical exams are recommended to improve recognition.

Neuroleptic drug induced psychotic relapse ("supersensitivity psychosis")

Chouinard G. Severe cases of neuroleptic-induced supersensitivity psychosis. Diagnostic criteria for the disorder and its treatment. Schizophr Res 1991 Jul-Aug;5(1):21-33 Psychiatric Research Center, Louis-H. Lafontaine Hospital, University of Montreal, Quebec, Canada.

ABSTRACT: Tardive dyskinesia is thought to result from neostriatal dopaminergic receptor supersensitivity induced by chronic treatment with neuroleptics. Similarly, receptor supersensitivity occurring in other dopaminergic regions of the brain could result in the development of supersensitivity psychosis. As with tardive dyskinesia, severe forms of the disorder are rare. Ten such cases are described whose main characteristic is that psychotic symptoms can no longer be masked by increased dosages of neuroleptics. Diagnostic criteria for the disorder are proposed, and treatment with antiepileptic medication is described.

Kirkpatrick B, Alphs L, Buchanan RW (1992) The concept of supersensitivity psychosis. J Nerv Ment Dis 1992 Apr;180(4):265-70. Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore 21228.

ABSTRACT: The hypothesis that chronic neuroleptic treatment may induce

relapse in s chizophrenic patients has received considerable attention. This effect, usu led supersensitivity psychosis, has been attributed to neuroleptic ed changes in mesolimbic or mesocortical dopaminergic receptors. H er, research has not established that neuroleptics cause the proposed e and considerations of mechanism have not been separated from those of ca n. The focus of research in this area should be the establishment or refutatic causal relationship between chronic neuroleptic use and psychotic relapse.

Chouinard G, Sultan S. Treatment of supersensitivity psychosis withantiepileptic drugs: report of a series of 43 cases. Psychopharmacol Bull 1990;26(3):337-41. Allan Memorial Institute, Montreal, Quebec, Canada.

Supersensitivity psychosis has emerged as a potential side effect of long-term neuroleptic therapy that may be similar to tardive dyskinesia. Schizophrenic patients with supersensitivity psychosis and considered to be drug-resistant were treated with anti-epileptic medication. Forty-three separate trials were conducted on a total of 35 patients. Over half improved on clinical global impression, some of them considerably. We propose that antiepileptic drugs ameliorate supersensitivity psychosis and so-called “drug-resistant” schizophrenic patients by correcting a pharmacological kindling effect in the limbic system which results from chronic neuroleptic therapy. Publication Types: Clinical trial

Kahne GJ. Rebound psychoses following the discontinuation of a high potency neuroleptic. Can J Psychiatry 1989 Apr;34(3):227-9

Increased familiarity with the effects of psychotropic medications has led to modifications in both prescribing habits and length of treatment. The case of a 34 year old woman is presented, in whom the return of psychotic symptoms following the discontinuation of neuroleptic medications is attributed to a rebound phenomena as opposed to a relapse of an underlying chronic illness

The author ... parallel situations previously described in the medical literature and outline ... nceptual framework for the understanding of this phenomenon.

Bowers ME ... vigar ME. Psychotic patients who become worse on neuroleptics. J Clin Psych ... rmacol 1988 Dec;8(6):417-21. Yale University School of Medicine, Departmer ... sychiatry, New Haven, Connecticut

ABSTRAC ... describe a group of psychotic patients who became worse early in the course of neuroleptic treatment. Characteristics of this group were: predominantly female sex, relatively brief onset, family history of affective disorder, hypomotoric presentation, and severe neuroleptic side effects. We propose that some patients with affective psychoses are uniquely susceptible to profound blockade of the nigrostriatal dopaminergic system by neuroleptics.

During the 1990s, the "Decade of the Brain:"

Newer "atypical" neuroleptics have been developed-clozapine, risperdone, olanzapine and quitepane-these drugs have a lower risk of EPS and TD, but are associated in varying degrees with sedation, cardiovascular and liver enzyme abnormalities, anticholinergic effects, extreme weight gain (30lbs to 50lbs) which significantly increases the risk for diabetes, sexual dysfunction, NMS, seizures, mania, and (in the case of clozapine) agranulocytosis.

Additionally, mounting clinical evidence and findings -from non-industry sponsored research-point to additional, severe, adverse neurological changes in response to long-term exposure to neuroleptics. These drugs' actions suppress certain brain receptors (e.g., dopamine, glutamate), and when such drugs are withdrawn (or a patient stops taking them) the drug-induced receptor changes are unmasked, causing an acute "discontinuation syndrome" (i.e., "rebound psychosis") that is often more severe than the original symptoms of the illness. Psychotic relapse can cause months of mental and emotional anguish and loss of functioning-rebound psychosis can cause violent and suicidal behavior in patients

not previou[illegible]lent. [Often, these drug-induced reactions are used to justify forcing the [illegible]n back on the drugs.]

Collaborati[illegible]rking Group on Clinical Trial Evaluations. Adverse effects of the atypical ar[illegible]hotics. J Clin Psychiatry 1998; 59 Suppl 12:17-22

ABSTRAC[illegible]erse effects of antipsychotics often lead to noncompliance. Thus, clinicians s[illegible]address patients' concerns about adverse effects and attempt to choose medications that will improve their patients' quality of life as well as overall health. The side effect profiles of the atypical antipsychotics are more advantageous than those of the conventional neuroleptics. Conventional agents are associated with unwanted central nervous system effects, including extrapyramidal symptoms (EPS), tardive dyskinesia, sedation, and possible impairment of some cognitive measures, as well as cardiac effects, orthostatic hypotension, hepatic changes, anticholinergic side effects, sexual dysfunction, and weight gain.

The newer atypical agents have a lower risk of EPS, but are associated in varying degrees with sedation, cardiovascular effects, anticholinergic effects, weight gain, sexual dysfunction, hepatic effects, lowered seizure threshold (primarily clozapine), and agranulocytosis (clozapine only). Since the incidence and severity of specific adverse effects differ among the various atypicals, the clinician should carefully consider which side effects are most likely to lead to the individual's dissatisfaction and noncompliance before choosing an antipsychotic for a particular patient.

Wyderski RJ, Starrett WG, Abou-Saif A. Fatal status epilepticus associated with olanzapine therapy. Ann Pharmacother 1999 Jul-Aug;33(7-8):787-9. Department of Internal Medicine, School of Medicine, Wright State University, Dayton, OH 45409, USA. rjwyderski@mvh.org

OBJECTIVE: To report a case of fatal status epilepticus in a patient using

olanzapine [illegible] no known underlying cause or predisposing factor for seizure. CASE SUM[illegible]: A 41-year-old white woman developed witnessed seizures at home that [illegible]ssed to status epilepticus. She subsequently died from secondary [illegible]omyolysis and disseminated intravascular coagulation.She had been takin[illegible]zapine for five months prior to the event. No other toxic, metabolic, [illegible]tomic abnormalities were identified pre- or postmortem to explain the[illegible]es. Her seizures were a probable adverse drug reaction based on the Naranjo scale.

DISCUSSION: This is the first case of fatal status epilepticus described that has been associated with the use of olanzapine. The pharmacodynamics of olanzapine are similar to those of clozapine, which has been described to induce seizures in 1-4% of patients. It is possible that this patient may have suffered seizures due to a similar effect. Alternate explanations include neuroleptic malignant syndrome and alcohol or benzodiazepine withdrawal seizures, although her clinical history does not suggest these etiologies.

CONCLUSIONS: Although olanzapine has infrequently been associated with seizures in premarketing studies, its potential to induce them exists. Postmarketing surveillance should continue to determine how significant this effect may be.

Drug induced “rebound psychosis” & Mania

Shore D. Clinical implications of clozapine discontinuation: report of an NIMH workshop. Schizophr Bull 1995;21(2):333-8. Division of Clinical and Treatment Research, NIMH, Rockville, MD 20857, USA.

ABSTRACT: In September 1994, the National Institute of Mental Health convened a group of scientists to discuss the clinical effects of rapid clozapine discontinuation, especially in light of the introduction of risperidone for the treatment of schizophrenia. Despite concern over recent reports of clinical

deterioratic ychotic exacerbations, somatic withdrawal symptoms, and extrapyran de effects) in a few patients abruptly discontinued from clozapine, s currently insufficient information to determine the magnitude of the probler ociated with clozapine withdrawal.

However, c ns are reminded that the withdrawal schedule for clozapine indicates a al tapering schedule (unless the patient is experiencing severe side effects switching patients from clozapine to risperidone does not mean that such tapering is unnecessary; and that the use of risperidone may not produce all of the same effects as clozapine in some treatment-refractory patients. PMID: 7543218, UI: 95357664

Stanilla JK, de Leon J, Simpson GM. Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. J Clin Psychiatry 1997 Jun;58(6):252-5. Department of Psychiatry, Allegheny University, Norristown State Hospital, Pa. 19401, USA.

BACKGROUND: Withdrawal symptoms for typical antipsychotics are generally mild, self-limited and do not include development of psychotic symptoms. In contrast, withdrawal symptoms for clozapine can be severe with rapid onset of agitation, abnormal movements, and psychotic symptoms. Different pathophysiologic etiologies have been suggested for these severe symptoms, including dopaminergic supersensitivity and rebound. METHOD: Three case reports of clozapine withdrawal symptoms are presented. A review of previous case reports and discussion of the etiology of withdrawal symptoms of typical antipsychotics and clozapine are provided.

RESULTS: These three patients developed delirium with psychotic symptoms that resolved rapidly and completely upon resumption of low doses of clozapine.

CONCLUSION: The severe agitation and psychotic symptoms after clozapine withdrawal in these three patients were due to delirium, perhaps the result of

central cho[illegible]c rebound. The withdrawal symptoms and delirium resolved rapidly wit[illegible]mption of low doses of clozapine. Severe withdrawal symptoms can probab[illegible]avoided by slowly tapering clozapine and/or simultaneously substitutin[illegible]her psychotropic with high anticholinergic activity, such as thioridazin[illegible]

Durst R, Te[illegible]m A, Katz G, Knobler HY (1999) Withdrawal from clozapine: the "rebound p[illegible]henon". Isr J Psychiatry Relat Sci 1999;36(2):122-8. Jerusalem Mental Health Center, Kfar Shaul Hospital, Israel.

Clozapine is an "atypical" antipsychotic agent for treating previously resistant schizophrenic patients. Its main advantages over "typical" neuroleptics are low incidence of extrapyramidal side effects and its capacity to induce therapeutic response in previously treated refractory patients. However, withdrawal from clozapine has been observed to lead to "atypical" clinical characteristics or a "rebound phenomenon," manifested in two interwoven clinical forms: (1) psychotic exacerbation, and (2) cholinergic rebound. The underlying pathophysiological mechanism of this phenomenon is postulated to be a result of cholinergic supersensitivity. In this paper, the "rebound phenomenon" will be discussed and exemplified by three case histories in which abrupt cessation of clozapine led to serious deterioration and psychotic exacerbation, and one case in which gradual titration from the drug was employed in order to preempt this hazardous occurrence. PMID: 10472746, UI: 99401971

Still DJ, Dorson PG, Crismon ML, Pousson C Effects of switching inpatients with treatment-resistant schizophrenia from clozapine to risperidone. Psychiatr Serv 1996 Dec;47(12):1382-4. Department of Psychiatry, Community Hospitals Indianapolis, IN 46219, USA.

A prospective, open-label study in a 400-bed state psychiatric hospital evaluated change in therapeutic response among ten patients with treatment-resistant

schizophre[illegible]io were switched from clozapine to risperidone. Drug effects were exam[illegible]efore discontinuation of clozapine and at three, six, nine, and 12 weeks of ri[illegible]one treatment. No patients improved, and five discontinued treatment [illegible]exacerbation of psychosis or adverse effects. Changes in scores on the Posi[illegible]d Negative Syndrome Scale, the Brief Psychiatric Rating Scale, and the Ba[illegible]kathisia Scale indicated clinically significant worsening of symptoms. [illegible]ndings do not support replacing clozapine with risperidone for patients with treatment-resistant schizophrenia.

Delassus-Guenault N, Jegouzo A, Odou P, Seguret T, Zangerlin H, Vignole E, Robert H. Clozapine-olanzapine: a potentially dangerous switch. A report of two cases. J Clin Pharm Ther 1999 Jun;24(3):191-5. Department of Pharmacy, EPSM Lille-Metropole, Armentieres, France.

BACKGROUND: Withdrawal symptoms associated with switch between two typical antipsychotics are generally rare and mild. In contrast, switching from clozapine to risperidone can be lead to severe withdrawal symptoms. Different pathophysiologic aetiologies have been suggested for explaining these severe symptoms, including cholinergic supersensitivity and rebound. Theoretically, the switch from clozapine to olanzapine should not lead to any problems because those two agents have the same affinity in vitro for muscarinic receptors. OBJECTIVE: This study reports two cases of switches from clozapine to olanzapine, in refractory schizophrenic patients, which were associated with severe withdrawal symptoms.

RESULTS: After the switch, the two patients developed diaphoresis, hypersialorrhea, bronchial obstruction, agitation, anxiety and enuresis. The symptoms were treated with anticholinergic medication and by an increase in dose of olanzapine to 20 mg/day. For one of the patients this treatment led to normalization of secretion. For the other patient, a superinfection leading to a bilateral pneumopathy which required emergency hospitalization in a general

hospital w[illegible]erved.

CONCLUSI[illegible]ne symptomatology and the response to treatment lead to the hypothesis [illegible]uscarinic from abrupt weaning. The withdrawal symptoms disappeare[illegible]dly with an increase in olanzapine dosage and with anticholine[illegible]arted at the beginning of the switch. We recommend slow clozapine w[illegible]g over 3 weeks or more with concurrent anticholinergic treatment.

Ekblom B, Eriksson K, Lindstrom LH. Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. Psychopharmacology (Berl) 1984;83(3):293-4.

In two patients with chronic schizophrenia, who were on clozapine medication for more than 6 months, a sudden withdrawal of the drug resulted in a very pronounced deterioration of the psychosis within 24-48 h. The most prominent symptoms were auditory hallucinations and persecutory ideas and one patient tried to commit suicide. These observations are interpreted as supersensitivity psychoses induced by the very effective clozapine treatment.

Jauss M, Schroder J, Pantel J, Bachmann S, Gerdsen I, Mundt C. Severe akathisia during olanzapine treatment of acute schizophrenia. Pharmacopsychiatry 1998 Jul;31(4):146-8. Department of Psychiatry, University of Heidelberg, Germany. Jauss@USA.net

Olanzapine is a newly developed atypical neuroleptic with a marked affinity to the 5-HT2, D2 and D4 dopamine receptors. Like other atypical neuroleptics olanzapine is considered to show a reduced prevalence of extrapyramidal side effects when compared to classical neuroleptic drugs.

We report on three patients with acute schizophrenia, who developed severe akathisia during treatment with olanzapine (20-25 mg/d). In two of these cases

akathisia r d after withdrawal of olanzapine and substitution by a classical or an atypi uroleptic agent, respectively. In one of these patients olanzapine was well to d when reintroduced in combination with lorazepam after complete r on of akathisia.

In the third t akathisia as sufficiently controlled by dose reduction. Akathisia is generall dered to result from D2 dopamine receptor antagonism. In the case of aty euroleptics such as olanzapine a low but still considerable D2 dopamine receptor occupancy may be compensated by the 5-HT2 antagonism. However, this mechanism may fail under certain circumstances, in particular if D2 dopamine antagonism exceeds a certain threshold. One should therefore be aware of possible extrapyramidal side effects with olanzapine that are reduced compared to classical neuroleptic drugs but not completely eliminated.

Molho ES, Factor SA (1999). Worsening of motor features of parkinsonism with olanzapine. Mov Disord 1999 Nov;14(6):1014-6. Department of Neurology, Albany Medical College, New York, USA.

Clozapine is the current treatment of choice for drug-induced psychosis (DIP) occurring in Parkinson's disease. However, alternative medications have been sought because of the small but significant risk of agranulocytosis and the need for frequent blood testing. The new "atypical" antipsychotic olanzapine (OLZ) has recently been proposed as a safe and effective option for treating psychosis in this setting. To investigate this, we retrospectively evaluated all 12 of our patients treated with OLZ for DIP. Symptoms of psychosis were improved in nine of 12 patients, but nine of 12 patients also experienced worsening of motor functioning while on OLZ. The worsening was considered dramatic in six of these patients. Overall, there was no significant increase in levodopa doses on OLZ. Only one patient remained on OLZ at the time of the analysis. Nine patients were switched to alternative treatment for DIP.

"We conclu t although Olanzapine may improve symptoms of psychosis in parkinsoni ents, it can also worsen motor functioning. In some patients, the degree of r worsening may be intolerable."

Life-thre ing neuroleptic malignant syndrome (NMS)

NMS is the of dopamine receptor blockade in the brain, induced by ALL neuroleptic [included is a sample of published NMS reports associated with the new, "atypical" drugs]

Karagianis JL, Phillips LC, Hogan KP, LeDrew KK. Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. Ann Pharmacother 1999 May;33(5):623-30. Memorial University of Newfoundland, St. John's, Canada.

BACKGROUND: Clozapine has recently been found to be associated with neuroleptic malignant syndrome (NMS). Our objective is to determine if clozapine causes NMS, if the presentation of clozapine-induced NMS differs from that of traditional agents, and which set of diagnostic criteria will most readily allow diagnosis of NMS associated with clozapine.

METHODS: Two new cases of clozapine-associated NMS are presented, along with previously reported cases from the literature, identified by using a MEDLINE search (1966-August 1998). From all cases, concomitant medications and washout periods were examined (if available) to assess clozapine as the likely cause of NMS. Characteristics of clozapine and traditional antipsychotic-induced NMS were compared. Different diagnostic criteria for NMS were applied to the cases to determine which were more likely to diagnose the syndrome.

RESULTS: Clozapine was deemed a highly probable cause of NMS in 14 cases, a medium probability cause in five cases, and a low probability cause in eight cases. The most commonly reported clinical features were tachycardia, mental status

changes, a phoresis. Fever, rigidity, and elevated creatine kinase were less prominent n NMS associated with classical neuroleptics.

CONCLUSI Clozapine appears to cause NMS, although the presentation may be differen that of traditional antipsychotics. Levenson's original and Addonizio' fied criteria were more likely to diagnose NMS than were other criteria. Clc e-associated NMS may present with fewer clinical features. Limitations e lack of detailed information provided by many of the case reports and the use of "modified" diagnostic criteria for retrospective diagnosis.

Amore M, Zazzeri N, Berardi D. Atypical neuroleptic malignant syndrome associated with clozapine treatment. Neuropsychobiology 1997;35(4):197-9. Institute of Psychiatry, University of Bologna, Italy.

Clozapine is an atypical neuroleptic drug that was initially thought not to cause neuroleptic malignant syndrome (NMS). The authors report a case of NMS associated with clozapine use, developed in a patient without previous history of NMS. Considering that 13 such cases (including ours) have been reported so far, NMS should be considered in the differential diagnosis of a febrile patient treated with clozapine.

Thornberg SA, Ereshefsky L. Neuroleptic malignant syndrome associated with clozapine monotherapy. Pharmacotherapy 1993 Sep-Oct;13(5):510-4. Clinical Psychiatric Pharmacy Program, University of Texas Health Science Center at San Antonio 78284-6220.

Abstract: Neuroleptic malignant syndrome is thought to be a result of dopamine receptor blockade in the striatum. Clozapine has only weak affinity for dopamine type 1 and 2 receptors, and therefore it was thought this drug would not precipitate the syndrome. However, six cases of the syndrome have been reported

in patients ing clozapine monotherapy. A review of the pathoetiology of symptoms ing in the syndrome is included.

Sachdev P, , Kneebone M, Kissane D. Clozapine-induced neuroleptic malignant me: review and report of new cases. J Clin Psychopharmacol 1995 Oct;1 65-71. Neuropsychiatric Institute, Prince Henry Hospital, Sydney, Australia.

The published case reports of clozapine-induced neuroleptic malignant syndrome (NMS) are reviewed, to which the authors add three, and possibly four, new cases seen in Australia, occurring in and estimated 1,250 patients exposed to the drug. The review suggests that typical NMS does occur with clozapine and that its incidence may be as common as with the classic neuroleptics. The features of clozapine-induced NMS may be somewhat different, with fewer extrapyramidal side effects and a lower rise in creatine kinase levels. The occurrence of NMS with clozapine raises important issues with regard to our understanding of the pathophysiology of the syndrome.

Margolese HC, et al. [See Related Articles] Olanzapine-induced neuroleptic malignant syndrome with mental retardation. Am J Psychiatry. 1999 Jul;156(7):1115-6. No abstract available.

Hickey C, et al. [See Related Articles] Olanzapine and NMS. Psychiatr Serv. 1999 Jun;50(6):836-7. No abstract available. PMID: 10375159; UI: 99301695.

Filice GA, M[illegible]gall BC, Ercan-Fang N, Billington CJ. Neuroleptic malignant syndrome [illegible]ated with olanzapine. Ann Pharmacother 1998 Nov;32(11)[illegible]-9. Infectious Disease Section, Veterans Affairs Medical Center, Minneapoli[illegible]55417, USA.

OBJECTIVE[illegible]port a case of neuroleptic malignant syndrome (NMS) associated with the us[illegible]anzapine. CASE SUMMARY: A 67-year-old white man with bipolar dis[illegible]leveloped nausea and vomiting. After 12 days, he became confused, delirious, and manic. His only medications were olanzapine 10 mg/d and divalproex sodium 500 mg bid. He was admitted to a hospital and treated for dehydration and mania. Olanzapine was given on 6 of the first 7 hospital days. On hospital day 6, typical NMS developed with the body temperature increasing to 39.9 degrees C, obtundation, rigidity, tremor, diaphoresis, fluctuating pupillary diameter, labile tachycardia and hypertension, hypernatremia, and elevated serum creatine kinase. Olanzapine was stopped after hospital day 7, and the syndrome resolved by hospital day 12.

DISCUSSION: The patient had all of the major manifestations of NMS. There was no other likely explanation for his illness and he received no other drug likely to be associated with the syndrome. This is the first case reported in which NMS was associated with olanzapine.

Apple JE, et al. [See Related Articles] Neuroleptic malignant syndrome associated with olanzapine therapy. Psychosomatics. 1999 May-Jun;40(3):267-8. No abstract available. PMID: 10341541; UI: 99273087.

Moltz DA, et al. [See Related Articles] Case report: possible neuroleptic malignant syndrome associated with olanzapine. J Clin Psychopharmacol. 1998 Dec;18(6):485-6. No abstract available. PMID: 9864084; UI: 99079788.

Burkhard P[illegible]l. [See Related Articles] Olanzapine-induced neuroleptic malignant [illegible]me. Arch Gen Psychiatry. 1999 Jan;56(1):101-2. No abstract available. P[illegible]9892264; UI: 99107282.

Johnson V, [illegible] See Related Articles] Neuroleptic malignant syndrome associated [illegible]lanzapine. Aust N Z J Psychiatry. 1998 Dec;32(6):884-6. PMID: 10084355; [illegible] 181846.

Gheorghiu S, et al. [See Related Articles] Recurrence of neuroleptic malignant syndrome with olanzapine treatment. Am J Psychiatry. 1999 Nov;156(11):1836. No abstract available. PMID: 10553758; UI: 20019186.

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1998 MRI Studies demonstrate structural brain changes in schizophrenia patients treated with both standard and "atypical" neuroleptic drugs:

Non-industry sponsored researchers are coming to realize that this rebound reaction to antipsychotic drugs-both standard and the newer atypicals– may be so great, it could be causing structural brain changes such as swelling of the brain. Gur, et al., (abstract below) conducted an NIMH-funded MRI imaging study to monitor changes in the size of the basal ganglia and thalamic regions of the brain in schizophrenia patients treated with neuroleptic drugs. They compared them to a group of patients who were never exposed to neuroleptic drugs, and to a group of healthy comparison subjects: As they put it: "Differences between groups and correlations between subcortical volumes and dose of medication indicate that exposure to neuroleptics is associated with hypertrophy...it appears that patients treated with neuroleptics show hypertrophy relative to their neuroleptic-naive counterparts and to healthy comparison subjects."

Neuroleptics increased the area of both regions of the brain: a higher dose of standard neuroleptics was associated with a size increase in multiple areas, while atypcal neuroleptics increased the volume only of the thalamic portion. The researchers also reported that increased size of these regions of the brain is associated with greater severity of symptoms: "For the neuroleptic-naive group, sub-cortical volumes were not correlated with severity of negative symptoms, but higher volumes of the thalamus and putamen were associated with more severe

positive sy[illegible]is...This association was evident for hallucinations...and bizarre behavior.... [illegible]eviously treated patients, higher subcortical volumes were associated [illegible]greater severity of both negative and positive symptoms."

VHS Comn[illegible]he researchers themselves say the brain changes visible in the MRI scan "[illegible]o be medication-induced hypertrophy."

In other wo[illegible]e patient's brains were being changed by the drugs in ways that would likely increase the severity of their disabling illness – and make it more difficult for them to ever withdraw from neuroleptic drugs.

The only ambiguity in these findings is the researchers reluctance to attribute all of the brain changes to neuroleptics. However, whether "hypertrophy could reflect structural adaptation to receptor blockade and may moderate the effects of neuroleptic treatment" does not lessen the damage caused to these patients.

Gur, R.E., Maany, V., Mozley, P.D., Swanson, C., Bilker, W., & Gur, R.C. (1998). Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. American Journal of Psychiatry, 155 (12), 1711-1717. [Study was funded by NIMH] For the full article online go to:http://ajp.psychiatryonline.org/cgi/content/full/155/12/1711#F1

ABSTRACT Objective: This study examined whether subcortical volumes of the basal ganglia and thalamus in schizophrenic patients are related to neuroleptic exposure and symptom severity. Method: Basal ganglia substructures and thalamic volumes were measured with magnetic resonance imaging in 96 patients with schizophrenia (50 men and 46 women) and 128 healthy comparison subjects (60 men and 68 women). Twenty-one of the patients were neuroleptic-naive; of the previously treated patients, 48 had received typical neuroleptics only, and 27 had received typical and atypical neuroleptics. The relation of volume measures to treatment status, exposure to neuroleptics, and symptoms was examined.

Results: The neuroleptic-naive patients did not differ from the healthy comparison subjects in subcortical volumes except for lower thalamic volume. In the neuroleptic-naive group, volumes did not correlate with severity of negative symptoms, but higher volumes in both the thalamus and the putamen were associated with more severe positive symptoms. The previously treated group showed higher volumes in the putamen and globus pallidus than the healthy comparison subjects and the neuroleptic-naive patients. In the treated group, a higher dose of a typical neuroleptic was associated with higher caudate, putamen, and thalamus volumes, whereas a higher dose of an atypical neuroleptic was associated only with higher thalamic volume. Higher subcortical volumes were mildly associated with greater severity of both negative and positive symptoms

Conclusions: Increased subcortical volumes in treated schizophrenic patients seem to be medication-induced hypertrophy. This hypertrophy could reflect structural adaptation to receptor blockade and may moderate the effects of neuroleptic treatment.

Chakos, M. berman, J.A., Bilder, R.M., Borenstein, M., Lerner, G., Bogerts, B., Wu, H., Kin & Ashtari, M. (1994). Increase in caudate nuclei volumes of first-episode sc renic patients taking antipsychotic drugs. American Journal of Psychiatry 0) 1430-1436.

Based on M easurements of patients who initially had under 12 weeks of lifetime exp to neuroleptics, and comparison with data after 18 months of treatment, thors concluded that "caudate enlargement occurs early in the course of treatment in young first-episode schizophrenic patients. This may be a result of an interaction between neuroleptic treatment and the plasticity of dopaminergic neuronal systems in young patients." It was known prior to this study that chronically treated patients had increased volumes in this portion of their brains, but it had been thought this was due to the disease and not the treatment.

Madsen Al, Keiding N, Karle A, Esbjerg S, Hemmingsen R: (1998) Neuroleptics in progressive structural brain abnormalities in psychiatric illness. The Lancet, 352 (9130) 784.

This was a longitudinal study of patients, some schizophrenic, some not, from the beginning of their treatment with neuroleptics until 5 years later. Before and after scans of the brain were done using computed tomography (CT). The finding was that diagnosis had no significant impact on the development of frontal atrophy, but that "the estimated risk of atrophy increases by 6.4% for each additional 10 g neuroleptic drug." [Complete text of article at the end of bibliog]

Gur, R.E, Cowell, P., Turetsky, B.I., Gallacher, F., Cannon, Bilker, W., & Gur, R.C. (1998) A follow-up magnetic resonance imaging study of schizophrenia. Archives

of General Psychiatry, 55 145-152.

This study looked at changes in the frontal and temporal lobes of the brains of schizophrenic patients over a period of about 31months. They found that for first episode patients, "higher medication dose was associated with greater reduction in frontal and temporal lobe volume r = -0.75 and -0.66 respectively; P<.001)." Volume reduction was associated with decline in some neurobehavioral functions.

Harrison P (1999) Review: the neuropathological effects of antipsychotic drugs, Schizophr Res 1999 Nov 30;40(2):87-99.

ABSTRACT: In addition to their neurochemical effects, antipsychotic (neuroleptic) drugs produce structural brain changes. This property is relevant not only for understanding the drugs' mode of action, but because it complicates morphological studies of schizophrenia. ÊHere the histological neuropathological effects of antipsychotics are reviewed, together with brief mention of those produced by other treatments sometimes used in schizophrenia (electroconvulsive shock, lithium and antidepressants)....The main alteration associated with antipsychotic medication concerns the ultrastructure and proportion of synaptic subpopulations in the caudate nucleus... The changes are indicative of a drug-induced synaptic plasticity, although the underlying mechanisms are poorly understood. Similarly, it is unclear whether the neuropathological features relate primarily to the therapeutic action of antipsychotics or, more likely, to their predisposition to cause tardive dyskinesia and other motor side-effects. Clozapine seems to cause lesser and somewhat different alterations than do typical antipsychotics, albeit based on few data. There is no good evidence that antipsychotics cause neuronal loss or gliosis, nor that they promote neurofibrillary tangle formation or other features of Alzheimer's disease.

The changes may be secondary to the effects of the antipsychotic drug on

dopamine [illegible]amate neurotransmitters. It is not yet clear what these changes mean· they [illegible]e related to the efficacy of the drug or may possibly be a marker for side eff[illegible]uch changes in living individuals could potentially provide an early mark[illegible]ardive dyskinesia and thus indicate which individuals should not take these [illegible] Virtually all the studies used Haldol, so it is not yet known whether cl[illegible]e or other newer antipsychotics may also produce these changes.

Tsai G, Goff DC, Chang RW, Flood J, Baer L, Coyle JT (1998) Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry 1998 Sep;155(9):1207-13 Department of Psychiatry, Harvard Medical School, Belmont, MA 02178, USA.

OBJECTIVE: Tardive dyskinesia is a movement disorder affecting 20%-40% of patients treated chronically with neuroleptic drugs. The dopamine supersensitivity hypothesis cannot account for the time course of tardive dyskinesia or for the persistence of tardive dyskinesia and the associated structural changes after neuroleptics are discontinued. The authors hypothesized that neuroleptics enhance striatal glutamatergic neurotransmission by blocking presynaptic dopamine receptors, which causes neuronal damage as a consequence of oxidative stress.

METHOD: CSF was obtained from 20 patients with schizophrenia, 11 of whom had tardive dyskinesia. Markers for oxidative stress, including superoxide dismutase, lipid hydroperoxide, and protein carbonyl groups, and markers for excitatory neurotransmission, including N-acetylaspartate, N-acetylaspartylglutamate, aspartate, and glutamate, were measured in the CSF specimens. Patients were also rated for tardive dyskinesia symptoms with the Abnormal Involuntary Movement Scale.

RESULTS: T[illegible]e dyskinesia patients had significantly higher concentrations of N-acetylas[illegible]e, N-acetylaspartylglutamate, and aspartate in their CSF than patients w[illegible]tardive dyskinesia when age and neuroleptic dose were controlled f[illegible]e significance of the higher levels of protein-oxidized products associated [illegible]ardive dyskinesia did not pass Bonferroni correction, however. Tardive dy[illegible]a symptoms correlated positively with markers of excitatory neurotrans[illegible]n and protein carbonyl group and negatively with CSF superoxide dismutase activity.

CONCLUSIONS: These findings suggest that there are elevated levels of oxidative stress and glutamatergic neurotransmission in tardive dyskinesia, both of which may be relevant to the pathophysiology of tardive dyskinesia.

Braus DF, Ende G, Weber-Fahr W, Sartorius A, Krier A, Hubrich-Ungureanu P, Ruf M, Stuck S, Henn FA (1999) Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. Schizophr Res 1999 Aug 23;39(1):19-29. Central Institute of Mental Health (ZI), NMR-Research, Mannheim, Germany.dfbraus@as200.zi-mannheim.de

Brain function and laterality in schizophrenia were investigated by means of a simple motor task with a self-generated left-hand sequential finger opposition (SFO) using a whole-brain high-speed functional imaging technique. Neuroleptic-naive, acutely ill schizophrenic patients were compared to schizophrenic patients under stable neuroleptic medication and matched controls. The goal was to evaluate both the motor function in first-episode patients and possible effects of different neuroleptic treatments on functional MRI results.

Forty schizophrenia patients matched in sex- and age to healthy volunteers participated in this study. All subjects underwent fMRI examinations on a conventional 1.5 T MR unit. The primary sensorimotor cortex and the high-order

supplemen motor area (SMA) were evaluated.

There was e similarity in the activation of the primary and high-order (SMA) sensorimot as between first-episode schizophrenic patients and controls. In contrast, a cant reduction in the overall blood oxygen level dependent (BOLD) res was seen in sensorimotor cortices in schizophrenic patients under stab lication with typical neuroleptics. This effect was not present in patients tre with atypical antipsychotics. Both antipsychotic treatments, however, led to a significant reduction in activation of the SMA region compared to controls and neuroleptic-naive subjects.

Thus, the present study provides no evidence for the localized involvement of the primary motor cortex or the SMA as a relatively stable vulnerability marker in schizophrenia. There is, however, strong evidence that neuroleptics themselves influence fMRI activation patterns and that there are major differences between typical neuroleptics and atypical antipsychotics.

Benes FM (1999) Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. Biol Psychiatry 1999 Sep 1;46(5):589-99. Laboratory for The Program in Structural Neuroscience, McLean Hospital, Massachusetts

Recent postmortem studies have demonstrated subtle alterations in the hippocampal formation (HIPP) of patients with schizophrenia (SZ). These changes include a decreased density of neuron receptors and a neuroleptic-dose-related increase of receptor terminals. The researchers hypothesize that the brain receptor changes identified “could potentially involve excitotoxic damage to interneurons.” The researchers indicate that “the precise time frame for the induction of such an injury during pre- versus postnatal life cannot as yet be inferred from the available data.” These researchers do not entertain the possibility that the “induction of such an injury” might be the result of neuroleptic

drugs. Hov nothing in the data precludes such suspicion.

“These finc re consistent with reports of abnormal oscillatory rhythms and increased l netabolic activity in the HIPP of patients with schizophrenia. The fact that p with manic depression also show a decrease of NPs in CA2 suggests tl anges in the GABA system may not be related to a susceptibility gene for SZ er, these alterations could be associated with a nonspecific factor, such ress, experienced either early in life or much later during adolescence or adulthood. Presumably, there are also changes associated in other transmitter systems that may play a more specific role in establishing the SZ phenotype.”

McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, Shenton ME (1999). MRI anatomy of schizophrenia. Biol Psychiatry 1999 May 1;45(9):1099-119. Harvard Medical School, Department of Psychiatry, VA Medical Center, Brockton,Massachusetts 02401, USA.

This meta-analysis of 118 peer-reviewed controlled studies from 1987 to 1998 by Harvard investigators found overwhelming evidence of altered brain structure in schizophrenia patients.”Structural magnetic resonance imaging (MRI) data have provided much evidence in support of our current view that schizophrenia is a brain disorder with altered brain structure, and consequently involving more than a simple disturbance in neurotransmission.”

The temporal lobe was the brain region with the most consistently documented abnormalities. Volume decreases were found in 62% of 37 studies of whole temporal lobe, and in 81% of 16studies of the superior temporal gyrus (and in 100% with gray matter separately evaluated). Fully 77% of the 30 studies of the medial temporal lobe reported volume reduction in one or more of its constituent structures... Most data were consistent with a developmental model, but growing

evidence w npatible also with progressive, neurodegenerative features, suggesting o-hit" model of schizophrenia, for which a cellular hypothesis is discussed.

VHS Comn lthough almost all patients during the years under examination have been ed to neuroleptic drugs during various periods of their illness, the authors do not examine the possibility that these drugs may be a precipitating cause of the "two-hit" model of schizophrenia...

Casey DE (1999). Tardive dyskinesia and atypical antipsychotic drugs. Schizophrenia Research 1999 Mar 1;35 Suppl:S61-6. Mental Health Division, Veterans Affairs Medical Center, Portland, OR 97207, USA. daniel.casey@med.VA.gov

Typical antipsychotic agents produce central nervous system effects, especially extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). Nearly every patient who receives neuroleptic therapy has one or more identifiable risk factors for TD, among the most significant of which are older age, female gender, presence of EPS, diabetes mellitus, affective disorders, and certain parameters of neuroleptic exposure (i.e. dose and duration of therapy). The typical course of TD is a gradual onset after several years of drug therapy, followed by slow improvement or remission, but a large number of patients have persistent TD with irreversible symptoms. In the management of TD, the patient's mental status is of primary concern. Currently, no uniformly safe and effective therapies for TD exist, though a variety of therapeutic agents, including some of the atypical neuroleptics, have been reported to treat TD successfully in some patients. Because TD liability is so much lower with novel antipsychotic therapy, all patients who have TD or are at risk for TD, as well as EPS, should be considered candidates for switching to these

new drugs

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