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Tardive Dyskinesia in Schizophrenia is Associated with Prolactin-Related Sexual Disturbances

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Tardive dyskinesia (TD) may occur in never-medicated patients with psychotic illness, indicating the existence of non-medication, possibly disease-related, causes. We tested the hypothesis that, independent of the antipsychotic-induced rise in prolactin, the incidence of TD would be associated with the incidence of prolactin-related sexual disturbances (PRSD), which would be suggestive of a common pathology involving multiple dopamine tracts. Simple, global measures of TD and PRSD (loss of libido, amenorrhea, gynaecomastia, impotence, and galactorrhea) were rated in a prospective, observational European Health Outcomes Study (SOHO). New onset of TD and new onset of PRSD at 3, 6, and 12 months was analyzed in a risk set of 4263 patients using a Cox proportional hazard model yielding adjusted hazard ratios (aHR). Incidence of TD was significantly and linearly comorbid with the incidence of PRSD in both men and women. Compared to those with no PRSD, the risk for TD was 2.0 (95% CI: 1.1, 3.7) with one PRSD, 2.4 (95% CI: 1.3, 4.5) with two PRSD, and 3.6 (95% CI: 1.1, 11.8) with three PRSD. Associations were stronger in those who only had received prolactin-sparing medications (aHR per unit PRSD increase = 2.0, 95% CI: 1.2, 3.3) than in those who only had received prolactin-raising medications (aHR = 1.3, 95% CI: 0.9, 1.9). In people with schizophrenia, TD and PRSD show comorbidities that are independent of antipsychotic-induced alterations in plasma prolactin. This may suggest a shared, pandopaminergic pathological mechanism associated with schizophrenia itself, rather than only a medication effect.
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INTRODUCTION

Only a minority of patients with a diagnosis of schizophrenia develop tardive dyskinesia (TD) over the course of antipsychotic treatment, indicating that some individuals carry a particular vulnerability to this condition. Although treatment-emergent TD has been reported in patients taking antipsychotic medications, the condition also occurs in patients not exposed to antipsychotic medication (Fenton *et al*, 1994). Therefore, some of the causes contributing to the risk of TD are thought to be intrinsic to the disease itself, possibly in interaction with age-related changes in the dopamine system (van Os *et al*, 1997).

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Although the nigrostriatal pathway is central in theories on the causes of TD, any hypothesized pathophysiological mechanisms may well extend to other dopamine tracts. If this were true, the rate of TD should be associated with indicators of dysfunction of other dopamine tracts, suggesting that TD is only one indicator of a much more widespread, pandopaminergic dysfunctional state.

The tubero-infundibular dopamine pathway regulates, by inhibition, pituitary prolactin secretion, causing sexual adverse events such as loss of libido, amenorrhea, gynaecomastia, impotence, and galactorrhea (Haddad and Wieck, 2004; Halbreich *et al*, 2003; Knegtering *et al*, 2003). There is some evidence that TD is associated with a deviant neuroendocrine response following prolactin challenge (Csernansky *et al*, 1986; Monteleone *et al*, 1988). However, not all the evidence is conclusive. Some authors reported differential prolactin responses in women but not in men, (Glazer *et al*, 1981), whereas others found no dissimilarities in prolactin response between patients with and without TD (Asnis *et al*, 1979; Jeste *et al*, 1981; Tripodianakis *et al*, 1983).

As the above experimental studies may be sampling around small effect sizes producing inconsistent results, a

complementary epidemiological approach, focusing on prospective associations between evidence of abnormalities of the tubero-infundibular pathway and onset of TD in large samples, may be productive. While it is difficult to obtain plasma prolactin in large epidemiological studies, sexual disturbance may serve as an indirect measure. Although the sexual disturbances seen in schizophrenia are of multifactorial origin, and therefore only in part attributable to illness-related or medication-related prolactin levels (Haddad and Wieck, 2004; Halbreich *et al*, 2003; Knegtering *et al*, 2003), they may nevertheless serve as an indirect measure for prolactin elevation in epidemiological studies, in particular if numerous confounding variables can be adequately controlled for. In the current paper prospective data from a large cohort of patients treated in routine clinical settings was used to examine the incident comorbidities of prolactin-related sexual disturbances (PRSD) and TD, applying analytical methods for complete adjustment of multiple confounding factors. As any association between PRSD and TD may be caused by their joint dependency on antipsychotic medication, analyses were stratified depending on whether the prescribed antipsychotic was prolactin-sparing or prolactin-raising. We hypothesized that if the association between PRSD and TD were medication-induced, this should be more apparent in the group exposed to prolactin-raising medications and higher levels of PRSD. If, however, observed comorbidity between PRSD and TD were intrinsic to the psychotic illness itself, associations should be equally or more evident in the group prescribed prolactin-sparing medications with lower levels of PRSD.

METHODS

Design and Patients

The SOHO study is an ongoing, 3-year prospective, observational health outcome study of the treatment of schizophrenia in Europe. Data was collected using a data collection form with a selection of measures that considered simplicity and ease of use with no training requirement. Investigators assessed the TD and PRSD that they judged to be associated with antipsychotic drug treatment. The basis for both ratings was clinical judgement. TD was rated on a four-point scale: (1) not present, (2) present, but does not significantly interfere with patient's functioning or health–related quality of life, (3) present, and significantly interferes with patient's functioning or health–related quality of life, (4) present, and outweighs therapeutic effect.

Full details of the SOHO study design have been published previously (Haro *et al*, 2003). Ethics Committee approval and informed consent was obtained as required by national regulations.

PRSD and Validation of Association with Prolactin

Loss of libido, amenorrhea or other menstrual disturbance, gynaecomastia, galactorrhea, and impotence or sexual dysfunction were rated on the basis of clinical judgment on a three point scale: (1) not present, (2) present, (3) not applicable. In order to validate their hypothesized association with prolactin, a variable was constructed dividing patients into two groups: those prescribed prolactin-raising medications (all first-generation oral and depot antipsychotics [FGA], risperidone, and amisulpiride) after each of the four visits over the 12-month period, and patients prescribed prolactin-sparing medications (all second-generation antipsychotics [SGA] except risperidone and amisulpiride) after each of the four visits over the 12-month period (Haddad and Wieck, 2004; Knegtering *et al*, 2003). Associations between PRSD and the variable reflecting prolactin-raising or prolactin-sparing group (hereafter: antipsychotic-induced prolactin) were examined in order to test whether PRSD would be higher in those exposed to prolactin-raising medication.

Antipsychotic Medication and the Association between PRSD and TD

As any association between PRSD and TD may be caused by their joint dependency on antipsychotic medication as explained earlier, associations between PRSD and TD were examined for moderation by type of medication, again using the 'antipsychotic-induced prolactin' variable reflecting prescription of prolactin-sparing or prolactin-raising antipsychotics.

Data Analysis

Each individual had four observations: baseline, 3, 6, and 12-month follow-up. For the purpose of the analyses, TD and PRSD were treated as dichotomous outcomes as follows: TD: present = score 2, 3 or 4 *vs* not present = score 1; PRSD: present = score 2 *vs* not present = score 1 and 3. The 'not applicable' ratings for the PRSD were recoded 'not present' because the majority of subjects with a rating of 'not applicable' had been taking medication and therefore were per definition at risk of developing PRSD. The only item truly considered 'not applicable' was amenorrhea in men. PRSD was also expressed as a sum score indicating the number of PRSD (0, 1, 2, 3 or more).

In order to calculate the incidence rates of TD and PRSD, three time bands were constructed (baseline—3 months, 3–6 months, and 6–12 months). Each person was allocated person-time according to the interval from baseline to the visit in which a patient was diagnosed with TD or, if no such diagnosis was made, to the last visit.

Incidence rates for each time band were calculated by dividing the number of incident cases by the total person-years. The cumulative incidence of TD or PRSD was calculated by dividing the total number of incident cases of TD or PRSD by the total person-years.

In order to assess the degree of comorbidity between TD and PRSD, associations between 12-month incidence of TD and 12-month incidence of PRSD were calculated in a risk set free of TD and PRSD at baseline, using a Cox proportional hazard survival regression model of survival time without TD with PRSD as a time-varying covariate.

Adjustment by Propensity Score

Covariates were those agreed upon by the SOHO advisory board and included sex, age, age of first contact, body mass

index, first episode status, compliance, and country among others (full list of covariates available on request). In addition, guided by previous literature, the following time-varying variables measured at the time of TD and PRSD assessments at 3, 6, and 12 months were included (Caligiuri *et al*, 1997; Correll *et al*, 2004; Halbreich *et al*, 2003; Lieberman *et al*, 1994; van Os *et al*, 2000; Yuen *et al*, 1996): treatment with SGA or FGA (pre- and post-assessment occasion), Clinical Global Impression positive, negative, cognitive, and depressive symptoms, other medications such as antidepressants, anticholinergics, and mood stabilizers. Approximately 80% of the sample was included in the model with all covariates, due to missing values in the covariates. As there were many confounding variables included in the models, traditional control for confounding by inclusion of covariates in the model may not be sufficient, as the degree of 'control' afforded by such models depends on the overlap in characteristics between the two outcome groups. The use of the propensity score has been suggested as a means to obtain more complete control (Joffe and Rosenbaum, 1999; Rubin, 1997) in these circumstances. A 'propensity score' is a model-based predicted probability of being exposed (in this case, of being in the group with sexual side effects). Predictors in the model are all of the potential confounding variables (ie characteristics on which the groups differ). Instead of controlling for a long list of confounders, the propensity score itself is controlled for, thus effectively controlling for *all* of the covariates included in the propensity models, and minimizing the loss of degrees of freedom in controlling for confounders.

Associations between PRSD and TD were expressed as incidence rate ratios and Cox proportional hazard ratios (unadjusted: HR; adjusted: aHR), together with their 95% confidence intervals. Interactions with sex and the antipsychotic-induced prolactin variable were assessed by Wald test (Clayton and Hills, 1993). Reported probability values for the predictor variable reflect two-sided tests of the null hypothesis of no association. All analyses were performed using the computer package STATA, version 9.1 (StataCorp., 2005).

RESULTS

Baseline Characteristics

A total of 9645 patients had non-missing data for PRSD and TD at baseline. The prevalence of TD in these 9645 was 898 (9.3%), and the prevalence of any PRSD was 5139 (53.3%); loss of libido: 45.6%; impotence or sexual dysfunction: 33.5%, gynaecomastia: 3.1%, galactorrhea 2.0%; amenorrhea in women: 25.6%. The risk set of patients without TD and without PRSD at baseline consisted of 4263 individuals. The mean age of these 4263 was 38.8 years (SD = 13.5), 58.9% were men, 16.4% were first episode and 34.4% had been exposed to an SGA in the 6 months before enrolment. After the baseline assessment, the proportion exposed to SGA rose to 85.0%. The number of individuals in the risk set prescribed prolactin-raising medication at all visits post-baseline was 1216 (40%), and the number prescribed prolactin-sparing medications at all visits post-baseline was 1812 (60%).

PRSD and Validation of Association with Prolactin

Over the follow-up period, there were 1162 incident cases of PRSD (loss of libido: 936; impotence or sexual dysfunction: 612; gynaecomastia: 60; galactorrhea: 41; amenorrhea in women: 198). Of the 1162 patients presenting with incident PRSD, 784 had one, 519 had two, and 68 had three PRSD. The incidence of PRSD was 37.0% (95% CI: 34.9, 39.2), and higher in the group prescribed only prolactin-raising medications (43%, 95% CI: 39–48) than in the group prescribed only prolactin-sparing medications (32%, 95% CI: 29–35; $P < 0.001$).

Incidence of TD

Over the follow-up period, there were 95 incident cases of TD, yielding a TD incidence rate of 2.6% (95% CI: 2.1, 3.2). The TD incidence was significantly comorbid with PRSD, independent of a range of confounders (Table 1). The sum score of incident PRSD and TD were associated with each other in a dose–response fashion: compared to those with

Table 1 Associations between Incident of TD and Incident of PRSD

	TD rate with PRSD[a]			TD rate without PRSD						
Type of PRSD	***n***	**Person-years**	**Rate (%)**	***n***	**Person-years**	**Rate (%)**	**HR[b] unadjusted[c] (95% CI)**	***P***	**HR adjusted (95% CI)**	***P***
Amenorrhea[d]	2	102	2.0	39	1387	2.8	0.7 (0.2, 3.0)	0.64	0.8 (0.2, 3.3)	0.73
Galactorrhea	1	18	5.5	91	3607	2.5	1.9 (0.3, 13.8)	0.52	[e]	
Impotence	23	341	6.8	71	3288	2.2	3.0 (1.9, 4.8)	0.000	2.3 (1.3, 4.0)	0.003
Loss of libido	31	521	6.0	63	3115	2.0	2.9 (1.9, 4.4)	0.000	2.4 (1.5, 3.9)	0.000
Gynaecomastia	3	30	10.0	91	3584	2.5	3.0 (0.9, 9.7)	0.06	3.2 (1.0, 10.6)	0.06
Any prolactin side effect	36	671	5.4	59	2999	2.0	2.6 (1.7, 4.0)	0.000	2.2 (1.4, 3.6)	0.001

[a]For example, first row: there were 198 women with incident amenorrhea. These 198 contributed 102 person-years follow-up time, whereas two developed TD. The rate therefore was 2%. Similarly, 1605 women without amenorrhea contributed 1387 person years, in which 39 developed TD, yielding a rate of 2.8%.
[b]Hazard ratio, a measure of relative risk.
[c]Adjusted for covariants agreed upon by the SOHO advisory board.
[d]Women only.
[e]Model would not converge/unstable estimate due to small numbers.

no PRSD (HR = 1), those with 1 PRSD (aHR = 2.0, 95% CI: 1.1, 3.7, $P = 0.024$), 2 PRSD (aHR = 2.4, 95% CI: 1.3, 4.5, $P = 0.008$), and 3 PRSD (aHR = 3.6, 95% CI: 1.1, 11.8, $P = 0.036$) were at progressively higher risk of developing TD (summary aHR linear trend: 1.6, 95% CI: 1.2, 2.0, $P = 0.001$). There were no interactions with sex (any PRSD excluding amenorrhea: $\chi^2 = 2.59$, $P = 0.11$).

Incidence of TD and Antipsychotic-Induced Prolactin

All the effect sizes of the association between PRSD and TD were larger in the group of individuals prescribed only prolactin-sparing medications, although formal comparisons between the two effects sizes remained statistically inconclusive by conventional alpha (Table 2).

DISCUSSION

A significant association was found between TD and sexual disturbances in patients with schizophrenia: the minority of individuals, who were at risk of developing TD, also displayed an elevated risk of developing PRSD.

In interpreting the results, it was assumed that loss of libido, impotence or sexual dysfunction, gynaecomastia, galactorrhea, and amenorrhea in women were prolactin-related to at least a degree. This, however, may be questioned, as many factors apart from prolactin may impact on these variables. For example, dopamine itself plays a role in general arousal (Paredes and Agmo, 2004) and antipsychotic-induced histaminergic, noradrenergic, alpha–blocking, and anticholinergic effects, as well as the effects of concomitant medication, all potentially influence sexual behaviour (Knegtering *et al*, 2003). Nevertheless, the validity of our exposure, in terms of it reflecting prolactin activity, is supported by (i) the simple and basic observation that patients reporting sexual dysfunctions on average have higher serum prolactin levels (Knegtering *et al*, 1999), and (ii) the fact that the current analyses did indeed confirm that PRSD were more common among those prescribed prolactin-raising medications. Furthermore, treatment-emergent sexual adverse events have been reported during treatment with antipsychotics known to elevate prolactin levels relatively specifically, suggesting prolactin may be related to the incidence of sexual dysfunction with a relatively small additional role suggested for histaminergic, noradrenergic, serotonergic, and cholinergic mechanisms (Knegtering *et al*, 2003). In addition, gynaecomastia, galactorrhea, and amenorrhea are among the clinical presentations more specifically associated with hyperprolactinaemia (Haddad and Wieck, 2004; Luciano, 1999).

Assuming that all PRSD variables are prolactin-related to a degree, arguably the simplest explanatory factor that can be evoked is that both PRSD and TD are caused by prolactin elevation induced by antipsychotic medications (Haddad and Wieck, 2004; Knegtering *et al*, 2003). However, this is unlikely as the association between TD and PRSD was, if anything, stronger rather than weaker for prolactin-sparing medications with a lower risk for both PRSD (Haddad and Wieck, 2004; Knegtering *et al*, 2003) and TD (Correll *et al*, 2004).

Therefore, although antipsychotic medication may well contribute separately to the onset of both TD and PRSD, the fact that survival without TD was at best only weakly associated with newly arising PRSD in those exposed to prolactin-raising medications suggests that the rise in prolactin, occasioned by antipsychotic medications, is not the common mechanism causing TD and PRSD to cluster over time. This is not unexpected, given the fact that the rise in prolactin is related to interactions between antipsychotic medication and D2 receptors that are outside the blood–brain barrier (Kapur *et al*, 2002; Knegtering *et al*, 2005), whereas the onset of TD is likely to reflect the central effects of antipsychotic medication. In other words, prolactin-raising medications may contribute separately to the risk of both TD and PRSD in the long term, but if the mechanisms and 'incubation' periods for these two outcomes are different, they will not be associated in time-to-event analyses as presented here. In contrast, their simultaneous clustering over time in those exposed to prolactin-sparing medications suggests an underlying common and central vulnerability, involving more than one central dopamine

Table 2 Associations between Incidence of TD and Incidence of PRSD as a Function of Antipsychotic-Induced Prolactin

					Interaction[b]	
Type of PRSD	**HR[a] prolactin-raising (95% CI)**	***P***	**HR[a] prolactin-sparing (95% CI)**	***P***	**χ^2**	***P***
Amenorrhea[c]	0.5 (0.1, 3.5)	0.46	2.9 (0.4, 23.4)	0.32	1.51	0.21
Galactorrhea	[d]		[d]			
Impotence	1.4 (0.6, 3.2)	0.46	3.6 (1.2, 10.3)	0.02	1.98	0.16
Loss of libido	2.0 (1.0, 4.0)	0.05	2.3 (0.8, 6.6)	0.12	0.05	0.82
Gynaecomastia	2.3 (0.5, 10.6)	0.27	10.9 (1.4, 82.3)	0.02	1.39	0.24
Any prolactin side effect	1.9 (1.0, 3.7)	0.07	2.3 (0.8, 6.2)	0.11	0.11	0.74
Continuous prolactin score[e]	1.3 (0.9, 1.9)	0.15	2.0 (1.2, 3.3)	0.01	1.76	0.18

[a]Hazard ratio, a measure of relative risk.
[b]Tests whether HR in the prolactin-raising group is significantly different from the HR in the prolactin-sparing group.
[c]Women only.
[d]Model would not converge/unstable estimate due to small numbers.
[e]Number of PRSD (0, 1, 2, 3, or more).

tract, that may be intrinsic to schizophrenia itself, and only detectable in the absence of external agents causing substantial increases in plasma prolactin that overshadow this internal, illness-related, association. Indeed, a recent investigation reported pituitary enlargement in never-medicated patients with schizophrenia, compatible with the hypothesis of a central, illness-related, mechanism (Pariante *et al*, 2005). Similarly, a recent report found high prolactin levels in a paranoid subgroup of never-medicated psychotic patients, suggestive of the existence of subtypes of psychotic illness associated with differences in dopaminergic tone (Segal *et al*, 2004). Another possible explanation may reside in differential D2 sensitivity in groups with and without TD (Shim *et al*, 2005). However, none of the above research findings provides a direct explanation for the association between PRSD and TD. Two basic, non-exclusive, types of explanations are possible. The first is that the same cause contributes to the onset of two conditions with different underlying pathologies. For example, stress is the most prevalent systemic condition associated with hyperprolactinaemia (Halbreich *et al*, 2003), and may be associated with TD through a mechanism involving raised cortisol levels (Aleem *et al*, 1988) or a mechanism involving modulation of the dopamine receptor by estrogen and its diverse and complex influences on prolactin levels (Halbreich *et al*, 2003; Turrone *et al*, 2000). The second explanation is that the same underlying pathology can be expressed pleiotropically as both TD and sexual disturbances, as both have been observed to be more prevalent in unmedicated patients with schizophrenia (Aizenberg *et al*, 1995; Fenton *et al*, 1994; Gregory, 1957), possibly indicative of a pandopaminergic dysfunction related to schizophrenia itself. Although it is not possible to distinguish between the two models on the basis of the current data, the latter explanation is the most parsimonious.

The results should be interpreted in the light of several methodological limitations.

Our data derives from an observational study in which the investigator 'observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice.' Controlling the therapy beyond normal medical practice also applies to the measures used to evaluate the pathology of interest or invasive procedures like blood monitoring (CPMP, 1996). By implication, this means that the current study relied on PRSD as a derived measure for prolactin. Many underlying causes may contribute to hyperprolactinaemia such as, for example, systemic conditions (eg cirrhosis, chronic renal failure or meningiomas) and non-psychotropic medications acting on the CNS (eg verapamil, estrogens, and other substances (Halbreich *et al*, 2003). However, the prevalences of these alternative causes are probably very low in our sample, and unlikely to have affected the current analysis in a non-random way. Similarly, sexual functioning is influenced by many factors other than hyperprolactinaemia such as demographic factors (Nazareth *et al*, 2003) and chronic medical conditions like hypertension and diabetes (Guay *et al*, 1999). Therefore, it is possible that, instead of prolactin, some of these other complex and interacting factors actually drive variation of sexual functioning and are associated with the incidence of TD, in spite of the extensive list of covariates used in the analyses.

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