

How Prevalent Are Anxiety Disorders in Schizophrenia? A Meta-Analysis and Critical Review on a Significant Association

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Objective: The presence of anxiety disorders (AD) in schizophrenia (SZ) is attracting increasing interest. However, published studies have yielded very broad variations in prevalence rates across studies. The current meta-analysis sought to (1) investigate the prevalence of co-occurring AD in SZ by reporting pooled prevalence rates and (2) identify potential sources of variations in reported rates that could guide our efforts to identify and treat these co-occurring disorders in patients with SZ. **Methods:** We performed a systematic search of studies reporting prevalence of AD in SZ and related psychotic disorders. Mean prevalence rates and 95% confidence intervals (CIs) were first computed for each disorder. We then examined the impact of potential moderators related to patient sampling or to AD assessment methods on these rates. **Results:** Fifty-two eligible studies were identified. Pooled prevalence rates and CIs were 12.1% (7.0%–17.1%) for obsessive-compulsive disorders, 14.9% (8.1%–21.8%) for social phobia, 10.9% (2.9%–18.8%) for generalized AD, 9.8% (4.3%–15.4%) for panic disorders, and 12.4% (4.0%–20.8%) for post-traumatic stress disorders. For all disorders, we found significant heterogeneity in rates across studies. This heterogeneity could at least partially be explained by the effect of moderator variables related to patient characteristics or assessment methods. **Conclusions:** AD are highly prevalent in SZ, but important variations in rates are observed between studies. This meta-analysis highlights several factors that affect risk for, or detection of AD in SZ, and could, thus, have an important impact on treatment and outcome of SZ patients.

Key words: OCD/PTSD/social anxiety/panic disorder/agoraphobia/phobia

Introduction

Though the recognition of co-occurrence of anxiety disorders (AD) in schizophrenia (SZ) dates back to the early years of psychiatric nosology,¹ the topic has long been neglected in both research and clinical settings. At least two factors may explain why such co-occurrence has only recently begun garnering attention. First, the diagnostic hierarchy rules in the *Diagnostic and Statistic Manual of Mental Disorders (DSM)* have evolved and are now less restrictive regarding diagnoses of AD in someone with SZ. *Diagnostic and Statistic Manual of Mental Disorders, Third Edition (DSM-III)* allowed an AD diagnosis only if it were clearly “not due to” another axis I disorder such as SZ, often leading to the underdiagnosis and undertreatment of AD in people with SZ.² The criteria became less restrictive with the *Diagnostic and Statistic Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)*, which allowed for the diagnosis of comorbid AD as long as the anxiety symptoms were “unrelated to” the main diagnosis. The current *Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV)*, criteria have evolved further, allowing a diagnosis of AD if the anxiety symptoms are “not better accounted for” or “not restricted to” SZ symptoms.

Second, there is an increasing awareness that positive outcomes can be achieved by a significant proportion of SZ patients, and current treatment approaches favor individualized care and adopt a more holistic perspective. Because recent evidence shows that comorbid AD have a negative impact on patients' recovery and functioning,^{3–12} recognizing and treating AD when present in patients with SZ spectrum could contribute to achieve more positive outcomes.^{13–15}

Several articles now report high prevalence rates for the different AD in people with psychosis, although rates vary strikingly across studies. Even if some sources of variation have been previously discussed (eg, the suspension or not of diagnostic hierarchy rules²), we are unaware of any systematic review quantitatively assessing methodological

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explanations for these variations in rates. Hence, using published reports on rates of AD in patients with psychoses, the aims of the current meta-analysis were (1) to calculate a pooled prevalence rate for each AD in SZ and (2) to examine the potential role of methodological variations related to patient sampling or to the AD assessment methods in explaining these variations across studies.

Methods

Search Strategy

Relevant articles (published before May 2009) were located through searches in Pubmed/Medline, and additional references were obtained by scrutinizing bibliographies of relevant articles and lists of articles citing these articles according to the science citation index (<http://portal.isiknowledge.com>).

Inclusion Criteria

The criteria to include relevant articles in this review were (1) focusing on schizophrenia spectrum psychotic disorder (SZSPD) diagnoses (including SZ, schizoaffective, schizophreniform and delusional disorders, and psychosis not otherwise specified) according to standardized diagnostic criteria (eg, *DSM-IV*); thus, studies were rejected if they included bipolar patients unless AD prevalence was reported separately for patients with SZSPD; (2) use of standardized criteria to diagnose comorbid AD (including obsessive-compulsive disorder [OCD], panic disorder [PD], agoraphobia [AGO], post-traumatic stress disorder [PTSD], social phobia [SP], simple phobia [SPP], and generalized anxiety disorder [GAD]); thus, we excluded studies reporting prevalence rates for anxiety symptoms instead of AD or if the diagnoses were based on self-report measures and/or on a cutoff score on a scale instead of diagnostic criteria; (3) reporting sufficient data to extract the prevalence rate for at least one comorbid AD in SZSPD patients. Short reports were included, but abstracts were excluded. Whenever 2 relevant articles reported on the same patients, only the article with the largest patient group was included (eg, we included data from Sim *et al.*¹⁶ but not from their previous paper¹⁷).

Moderator Variables of Interest

The variables thought to be potential moderating factors to the prevalence rates were grouped into those related to sampling (ie, patients' characteristics) and those related to assessment methods. The potential moderators related to sampling included: (1) the "Systematic" vs "Not systematic" sampling method; systematic sampling was defined as including either prevalent cases probability sampled from the whole population or incident cases systematically sampled from a given catchment area; studies not meeting this criteria were considered as Not systematic; (2) the breadth of SZSPD diagnoses ("SZ only" vs

"SZ and other SZSPD"); (3) the outpatient vs inpatient status; (4) the proportion of male; (5) the mean patients' age; and (6) the stage of illness ("first-episode psychosis" [FEP] vs "not FEP"). FEP was defined broadly to include all studies that reported recruiting patients within the first 5 years of illness.

The moderator variables of interest related to AD assessment included: (1) the diagnostic instrument, ie, the inclusion or not of the Structured Clinical Interview for *DSM* Disorders (SCID), which was the only instrument used in enough studies to yield meaningful comparisons; (2) the studies using the SCID were then divided according to whether they supplemented it with another instrument or not (eg, using the SCID and the Yale-Brown Obsessive Compulsive Scale^{18,19} for OCD); (3) the criteria used to diagnose comorbid AD (*DSM-III-R* vs *DSM-IV*, *DSM-III* could not be included because only two studies used these criteria); (4) the suspension or not of the diagnostic hierarchy rules; (5) finally, two studies allowed diagnoses of PTSD resulting from a trauma related to psychosis and its treatment, such as the experience of threatening hallucinations or use of coercive measures; because such diagnoses are not universally accepted, we examined whether the PTSD rates were higher in these two studies than in the other studies performed in SZSPD.

In addition, a few studies reported rates of AD separately for men vs women or for patients with a primary diagnosis of SZ vs schizoaffective disorder, and we also assessed the effect of these two within-study variables.

Statistical Analyses

The statistical analyses were performed following Fleiss²⁰ method to derive from several studies mean prevalence estimates with appropriate variance. The first step was to combine all the relevant studies to calculate a mean prevalence rate for each of the 7 AD, taking the size of each group into account. The 95% confidence interval (CI) of the mean proportion was also calculated, taking into account that the pooled variance of this mean proportion was derived from several independent proportions each having a different sample size. A chi-square with number of studies (*m*) minus 1 degree of freedom was then used to estimate the heterogeneity of the reported prevalence rates for each AD.

To assess differences in proportions between the 2 categories of each moderator variable we computed, for each category, the mean prevalence, the CI, and the heterogeneity statistic as described above. Then, both categories were compared using a chi-square test with one degree of freedom,²⁰ taking into account the different study sizes. Although we performed the analyses for each AD and for each moderator variable, some of the calculations were performed on very few studies and should be interpreted cautiously. We must stress that in some instances the information needed to classify

the article into one category or another was missing which precluded including these studies in our assessment of the effect of some moderating variables. For the continuous variables (mean age, proportion of males), correlations based on all relevant studies were performed between these continuous variables of interest and the proportion of affected patients in the individual studies for each AD. Finally, a Mantel-Haenszel approach was used for the two variables for which within-study comparisons were possible (patients' gender, SZ vs SZSPD diagnosis). All tests were two sided and a P value of .05 was the threshold for statistical significance.

Results

Studies Included in the Meta-Analysis and Mean Prevalence Rates

Fifty-two studies including a total of 4,032 subjects met our inclusion criteria.^{2,5-12,16,21-62} (see also the Appendix) Five of these studies reported prevalence rates for all AD, whereas the other studies focused on one or a few AD.

For the computation of mean prevalence rates, we merged 1-year and lifetime prevalence rates rather than separating them as is usual given that (1) 23 of the 52 studies (44%) omitted to report which of these types of prevalence was computed, (2) only 8 of the 29 studies for which this information was available (28%) reported 1-year rates, and (3) visual inspection revealed lower 1-year vs lifetime rates only for GAD, an observation that was also supported by direct statistical comparisons (see table 3). For these reasons, we computed overall prevalence rates across all studies for each AD and treated the type of prevalence rate (lifetime vs 1 year) as a potential moderator variable.

The number of studies (m), total number of patients (n), prevalence rates (mean, CI, range), and heterogeneity statistics are reported for each AD in table 1 which also includes a category termed "ANY" representing the proportion of patients with at least one of the AD assessed in the study. Because the scope of AD diagnoses included showed important variations between studies, results for this category should be interpreted cautiously.

For every AD, table 1 reveals very broad variations across studies reflected by highly significant heterogeneity tests. Although our analyses showed that the mean prevalence rates significantly differed from 0 for all AD, these rates should be interpreted cautiously given such heterogeneity. The following sections target variables potentially contributing to those variations in rates.

Effect of Moderator Variables

Table 2 reveals several instances of statistically significant relationships between moderating sampling variables and AD rates and table 3 reveals significant relationships between AD rates and moderator variables related to methods used to diagnose them. In addition, the few studies

that reported AD prevalence rates separately for men vs women or for patients with a primary diagnosis of SZ vs schizoaffective disorder within the same study did not yield any significant moderating effect of these variables (results not shown).

The moderating variables taken one at a time could not fully explain heterogeneity because there were several instances of residual heterogeneity within the strata of studies defined according to these moderators. In other instances, the absence of significant heterogeneity within strata was probably due to the small number of studies. Thus, none of these methodological variations could fully explain variations across studies. Unfortunately, the limited number of studies for each AD, together with the lack of information concerning variables of interest in some of studies (eg, suspending or not hierarchy rules, using lifetime or current rates) prevented considering multiple sources of variation in the same analysis and restricted the number of studies that contributed to assessing the effect of some moderator variables.

Comparison With the Epidemiology of AD in the General Population

Determining whether AD rates reported in SZSPD populations differ from those in the general population is crucial to appraise potential etiological links between AD and SZ. For this purpose, we compared the AD rates of the current meta-analysis with those in the general population recently reported in the meta-analysis by Somers et al.⁶³ A first observation is that our rates were numerically higher than those reported by Somers et al for every AD, with rates ranging between 5.4% and 14.9% in this meta-analysis vs from 1.2% to 6.2% in the meta-analysis by Somers et al. Moreover, examining the degree of overlap between the 95% CI of the rates from both meta-analyses revealed nonoverlapping CI for OCD, PD, and SP, supporting that the rates for these disorders are higher in SZSPD than the lifetime rates found in the general population.

It is interesting to note that Somers et al. reported, as we did, significant heterogeneity of rates across studies for all AD and though they raised plausible methodological explanations for this heterogeneity, they did not provide statistical testing of these explanations, making it difficult to compare with the effects observed in this meta-analysis.

Discussion

Combining data from 52 studies and a total of 4,032 patients, this study revealed high prevalence rates for every AD in patients with SZSPD. Although these prevalence rates were highly heterogeneous, the mean rates were nonetheless significantly different from zero for each AD and were higher than those typically reported in the general population, with non-overlapping CIs at least for OCD, PD, and SP.

Table 1. Overall Prevalence Rates

	OCD	PD	AGO	PTSD	SP	SPP	GAD	ANY
No. of studies (<i>m</i>)	34	23	12	20	16	11	14	16
No. of patients (<i>n</i>)	3007	1393	862	1388	1259	925	939	958
Mean prevalence rate (%)	12.1	9.8	5.4	12.4	14.9	7.9	10.9	38.3
95% CI	7.0%–17.1%	4.3%–15.4%	0.2%–10.6%	4.0%–20.8%	8.1%–21.8%	1.9%–13.8%	2.9%–18.8%	26.3%–50.4%
Range	0.6%–55.0%	0.0%–35.0%	0.0%–27.5%	0.0%–51.4	3.6%–39.5%	0.0%–30.8%	0.0%–45%	10.4%–85.0%
Heterogeneity χ^2	317.98	162.79	83.52	294.09	127.37	80.78	142.52	146.23
Heterogeneity <i>P</i>	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

Note: Bold values express main results. OCD, obsessive-compulsive disorder; PD, panic disorder; AGO, agoraphobia; PTSD, post-traumatic stress disorder; SP, social phobia; SPP, simple phobia; GAD, generalized anxiety disorder; ANY, proportion of patients with at least one of the anxiety disorders assessed in the study; CI, confidence interval. Our strategy to report overall prevalence rates across all studies reflect our recognition that several factors influence these rates and that the traditional distinction between 1-y vs lifetime rates (reported in table 3) is only one among other factors.

Because the *DSM* criteria for every AD involve having anxiety symptoms that are associated with distress and/or impairment in functioning, by definition a person for whom a comorbid AD diagnosis is attributed has been identified as carrying an additional burden. This additional burden was also explicitly assessed in a few studies that have directly contrasted functional outcome in SZSPD patients with or without an associated AD, greater impairment in quality of life and functioning being consistently observed in patients with comorbid AD.^{5–12}

Together, these observations and those of the current meta-analysis stress the importance of considering, in clinical settings and in research, co-occurring AD in SZSPD. Although this meta-analysis presents pooled AD rates, these should be interpreted cautiously given statistically significant evidence of heterogeneity in rates across studies and very broad CIs for all AD. These variations were thereafter studied by considering the effect of several moderator variables.

Impact of Moderator Variables

Together, the results from this meta-analysis point to a combination of factors influencing AD rates in SZSPD. All the moderator variables considered in this meta-analysis had a significant effect on the rate of at least one AD, and conversely, the rate of every AD was affected by at least one of the variables, highlighting the importance of these methodological choices for our understanding of the AD/SZSPD comorbidity. Although further studies will certainly provide a better understanding of the unique effect of each individual variable and of how these factors interact to influence the likelihood of observing AD in SZSPD, this meta-analysis nevertheless brings to light the effect of several factors.

Some factors are of particular relevance to clinicians. For example, the greater AD rates in studies that supplemented the SCID with additional instruments suggest

that there could be a benefit to asking more specific questions when trying to detect whether a patient presents with a co-occurring AD. For psychotic patients evaluated while hospitalized, it could also be worthwhile to reassess AD after psychosis has abated because anxiety symptoms might then be more easily differentiated from psychotic symptoms, which could explain the greater rates in outpatients. In the same vein, clinicians should be sensitive to the increased prevalence of AD in certain SZ patient populations, eg, in patient with a primary diagnosis of SZ (relative to other SZSDP) and in women.

In addition, the moderator variables addressed in the meta-analysis should definitely be taken into account for future research. The fact that the information required to classify the studies in one category or the other was often missing suggests that such information was not considered essential or pertinent in several previous studies. In light of our results, it is now clear that these factors do have an influence and should minimally be more clearly reported in future reports.

An illustration of the effect of not reporting some important information, combined with the other methodological choices of the different studies who did report this information, is the higher 1-year relative to lifetime OCD rate. This effect cannot reflect the reality because 1-year disorders would also count as lifetime disorders. Several other factors could, thus, have contributed to this effect. One that is noteworthy is that the three 1-year studies of OCD were the only ones to use the MINI International Neuropsychiatric Interview (MINI)⁶⁴ or the Anxiety Disorder Interview Schedule (ADIS-IV)⁶⁵ to diagnose OCD. Although these studies did not report suspending the diagnostic hierarchy, these rules are not explicitly rated in the MINI and could be easily overlooked, which would explain the higher prevalence observed when relying on this instrument. As for the ADIS, the higher rates could also be related to the more specific questions included

Table 2. Effect of the Variables Related to Patients Sampling

	OCD	PD	AGO	PTSD	SP	SPP	GAD
Systematic vs Non-systematic							
Systematic (%/m)	8.4/3	9.1/4	22.2/2	14.4/3	38.6/2	30.4/2	26.6/2
Not systematic (%/m)	12.4/31	10.0/19	4.3/10	12.0/17	13.9/14	6.5/9	9.9/12
Difference (χ^2)	3.54	0.23	30.63	0.97	23.86	38.47	14.16
<i>P</i> value (2 tailed)	NS	NS	<.001	NS	<.001	<.001	<.001
SZ only vs SZ and other							
SZ only (%/m)	11.3/15	16.3/10	7.8/4	21.8/8	12.9/6	9.5/3	16.7/6
SZ and other (%/m)	12.9/19	7.3/13	3.8/8	7.8/12	16.6/10	7.0/8	7.9/8
Difference (χ^2)	1.96	25.91	6.44	54.77	3.35	1.69	16.37
<i>P</i> value (2 tailed)	NS	<.001	.022	<.001	NS	NS	<.001
OP vs IP							
OP (%/m)	16.9/11	11.9/12	5.6/7	14.1/13	22.8/9	5.8/6	7.1/8
IP (%/m)	10.7/14	6.3/5	5.6/4	15.2/4	8.7/5	10.5/3	11.3/3
Difference (χ^2)	15.03	8.50	0.00	0.15	38.67	5.26	2.91
<i>P</i> value (2 tailed)	<.001	.007	NS	NS	<.001	.044	NS
Percentage of men in the sample							
<i>m</i>	29	17	8	14	13	8	11
<i>R</i>	-.21	-.22	-.24	-.65	-.28	-.59	-.42
<i>P</i> value	NS	NS	NS	0.012	NS	NS	NS
Mean age							
<i>m</i>	32	20	10	15	14	9	12
<i>R</i>	.06	.45	.36	.32	.29	-.69 ^a	-.49
<i>P</i> value	NS	.045	NS	NS	NS	.038	NS
FEP vs Not FEP							
FEP (%/m)	8.0/6	3.2/3	0.0/2	9.8/3	13.4/2	NA/0	0.0/1
Not FEP (%/m)	13.0/28	11.8/20	6.0/10	12.9/7	15.2/14	07.9/11	11.6/13
Difference (χ^2)	11.04	19.94	5.52	1.61	0.47	NA	7.80
<i>P</i> value (2 tailed)	.002	<.001	.038	NS	NS	NA	.010

Note: OCD, obsessive-compulsive disorder; PD, panic disorder; AGO, agoraphobia; PTSD, post-traumatic stress disorder; SP, social phobia; SPP, simple phobia; GAD, generalized anxiety disorder; m, number of studies; SZ, schizophrenia; OP, outpatients; IP, inpatients; FEP, first-episode psychosis; NS = $P > .1$; NA, not applicable.

^aThis counterintuitive effect is driven by one study in adolescents with SZ. When that study is disregarded, the correlation becomes positive although nonsignificant ($r = .17$).

for diverse obsessions or compulsions, in line with the increased detection of OCD for studies supplementing the SCID with instruments targeting specific OCD symptoms.

The effect of the instruments or gate questions used to diagnose AD is definitely an issue that would require more attention. These instruments can vary greatly in terms of the ability to detect anxiety symptoms meeting the criteria for the different disorders, and also to determine if the anxiety symptoms meet the criteria for a functional impact associated to those symptoms, and how both the symptoms and the functional impact can be distinguished from the symptoms and impact of psychosis. Future studies directly addressing the impact of combining additional instruments and/or additional sources of information (ie, relatives or caregivers, medical records) on the sensitivity of AD detection would be of great relevance in both clinical and research settings.

A related issue that will require particular attention is the way of dealing with the diagnostic hierarchy rules. Making AD diagnoses in subjects suffering from psychotic disorders is often difficult due to the challenge related to distinguishing AD from SZ symptoms (eg, intrusive and repetitive delusional ideas vs obsessions in OCD; hallucinatory experiences vs flashbacks in PTSD; delusional ideas of reference vs fear of being judged in SP) or in determining whether or not the anxiety symptoms and their functional impact is “not better accounted for” or “not restricted to” SZ. In the meta-analysis, we contrasted studies that reported suspending or not suspending the diagnostic hierarchy rule, but in reality, there is probably a continuum of strictness in the application of these rules, each study falling at different points on the continuum. To address this issue, future studies should provide more information on how the distinctions were made. For example, were the AD

Table 3. Effect of the Variables Related to Assessment of Comorbid Anxiety Disorders

	OCD	PD	AGO	PTSD	SP	SPP	GAD
Lifetime vs 1-y rates							
Lifetime (%/m)	8.3/14	11.7/11	7.1/7	14.0/9	11.0/7	14.8/6	24.8/5
1-y (%/m)	18.0/3	18.0/2	NA/0	13.8/5	15.7/2	NA/0	11.7/3
Difference (χ^2)	16.11	1.73	NA	0.01	1.80	NA	8.60
P value (2 tailed)	<.001	NS	NA	NS	NS	NA	.007
Used the SCID vs did not use the SCID							
Used the SCID (%/m)	13.1/23	8.3/15	1.8/7	5.5/9	15.7/9	2.8/7	3.9/6
No SCID (%/m)	10.5/11	16.0/8	10.8/5	19.1/11	13.5/7	17.5/4	22.8/8
Difference (χ^2)	4.62	14.72	32.97	58.92	1.08	62.16	80.79
P value (2 tailed)	.063	<.001	<.001	<.001	NS	<.001	<.001
Used only the SCID vs supplemented the SCID with other assessments							
SCID only (%/m)	7.8/12	7.9/12	0.8/5	3.8/7	13.3/7	2.2/5	2.8/4
SCID + other (%/m)	20.3/11	10.2/3	3.8/2	9.6/2	25.6/2	4.4/2	6.9/2
Difference (χ^2)	61.13	1.05	5.37	9.52	14.78	1.96	5.28
P value (2 tailed)	<.001	NS	.041	.004	<.001	NS	.043
Used the <i>DSM-IV</i> vs <i>DSM-III-R</i> criteria							
<i>DSM-IV</i> (%/m)	12.9/24	8.1/13	3.5/7	7.7/14	15.2/12	5.0/7	9.5/11
<i>DSM-III-R</i> (%/m)	8.6/9	11.5/8	8.0/5	23.7/6	14.3/4	12.9/4	17.8/2
Difference (χ^2)	10.44	4.15	8.33	67.23	0.16	18.52	7.55
P value (2 tailed)	.002	.083	.008	<.001	NS	<.001	.012
Diagnostic hierarchy suspended vs not suspended							
Suspended (%/m)	17.7/4	13.7/5	17.9/4	14.9/5	33.0/3	30.4/2	26.6/3
Not suspended (%/m)	18.4/7	19.4/1	0.0/1	NA/0	7.5/2	3.2/1	NA/0
Difference (χ^2)	0.03	0.65	6.46	NA	27.29	8.87	NA
P value (2 tailed)	NS	NS	.022	NA	<.001	.006	NA
PTSD diagnosis allowed for trauma related to psychosis versus not allowed							
Allowed (%/m)	NA	NA	NA	39.1/2	NA	NA	NA
Not allowed (%/m)	NA	NA	NA	9.13/18	NA	NA	NA
Difference (χ^2)	NA	NA	NA	111.17	NA	NA	NA
P value (2 tailed)	NA	NA	NA	<.001	NA	NA	NA

Note: OCD, obsessive-compulsive disorder; PD, panic disorder; AGO, agoraphobia; PTSD, post-traumatic stress disorder; SP, social phobia; SPP, simple phobia; GAD, generalized anxiety disorder; m, number of studies; SCID, Structured Clinical Interview for *DSM* Disorders; *DSM*, *Diagnostic and Statistic Manual of Mental Disorders*; NS = $P > .1$; NA, not applicable.

diagnoses given only when there was 100% confidence that the anxiety symptoms were not better accounted for by SZ symptoms or was a certain doubt allowed? A related issue is that of the reliability of the AD diagnoses. Given the difficulties linked to the determination of the presence or absence of AD in SZ, it is unfortunate that only 4 studies reported on the interrater reliability of the AD diagnoses (another 7 studies, however, used a consensus strategy to confirm AD diagnoses).

To summarize, there needs to be a consensus on how to assess the anxiety symptoms and their relationship with psychosis. Tables 2 and 3 show that this consensus is not yet reached and that this creates important differences in AD rates between studies. The discussion around the *Diagnostic and Statistic Manual of Mental Disorders, Fifth Edition (DSM-V)* offer a timely opportunity to clarify the hierarchy criteria or even consider adding anxiety as yet

another dimension or associated feature of psychosis. Cognitive symptoms are already being considered in this way for *DSM-V* with the argument that it “may increase clinicians’ awareness [of the condition], potentially leading to more accurate prognosis and better treatment outcome.”⁶⁶

In sum, it is hoped that the methodological aspects covered by the current review will be systematically assessed within the same group of patients in future studies or at least systematically described in future reports of AD in SZSPD to facilitate appraising potential sources of variations in results across studies and to guide our attempts to better delineate these disorders.

Recommendations for Future Studies

Although the current literature represents a first step to highlight the important co-occurrence of AD and

SZSPD, this meta-analytic review allowed us to identify other issues requiring further investigations. First, systematic assessments of SZSPD populations are needed to provide more accurate estimates of the prevalence of the SZ/AD comorbidity because most previous studies used convenience sampling, which is not optimal to estimate comorbidity rates. Moreover, of the 5 systematic sampling studies that reported AD rates in SZSPD, three were general population prevalence studies, which have certain drawbacks related to the assessment of comorbidities: (1) even large-scale studies such as the National Comorbidity Survey⁴³ have yielded sample sizes that were too small and relied on diagnostic tools that were not optimal to provide accurate and valid estimates of AD prevalence in SZ subjects; (2) these studies could also be problematic when it comes to validly detecting all cases of psychosis in their sample (ie, they tend to underestimate the prevalence of psychosis), and the sample identified might, thus, not be fully representative of the population of people affected with a psychosis. Moreover, some populations at high risk for SZ (eg, homeless people or inpatients) are particularly unlikely to be sampled in such studies. Hence, the best and most feasible alternatives are probably to sample subjects from large and comprehensive population registries (eg, psychiatric registries from Finland or Sweden) or to systematically sample FEP subjects within a given catchments area, which was attempted in a single study.^{32,55}

Second, given the broad variations in AD rates in general population studies, it is hoped that there will be future studies assessing with similar diagnostic methods both a psychotic disorder sample as well as a general population control sample to perform a more robust test of a possible elevation of AD rates in SZ.

Third, establishing that anxiety symptoms and their functional impact cannot be attributed to psychotic *symptoms* in SZSPD is just a first step toward establishing that these symptoms are at least to some extent independent of the psychotic *disorder*. Indeed, a second step in addressing this issue would be to determine whether AD occurring in SZSPD shares the other characteristics encountered in AD occurring in individuals without psychosis in terms of biological or cognitive markers or of other characteristic traits. Such an approach would contribute to increase confidence in the validity of such diagnoses derived in individuals with SZSPD. Other factors to take into account in this second step would include the timing of AD onset relative to that of psychosis, whether there is familial coaggregation of SZSPD and AD, and if there is, whether it is related to the presence of AD in SZSPD patients. For instance, finding that AD onset systematically occurs after that of psychosis could suggest that AD occur in SZSPD patients as a direct result of the psychotic experience or represent attenuated psychotic symptoms. Conversely, finding specific clinical or endophenotypic characteristics related to the presence of AD in patients and a familial co-aggregation specific to these

patients would suggest that such comorbidity reflects a specific subtype or dimension of psychotic illness.⁶⁷

Fourth, it would seem important to more systematically address the issue of whether or not targeted treatment of comorbid AD (ie, pharmacological or cognitive-behavioral therapy) lead to improved outcome in SZSPD given that AD (1) are highly prevalent in these patients, (2) have a negative on quality of life and functioning,⁵⁻¹² and (3) have been reported to hinder improvement in psychotic symptoms over time.¹⁶ A few studies have reported improvement of AD in SZSPD patients treated with cognitive-behavioral therapy and/or specific serotonin reuptake inhibitors.¹³⁻¹⁵

Strengths and Weaknesses

This meta-analysis not only allowed us to combine the results from 52 studies including a total of 4,032 patients but was also used to study the effects of several moderator variables that will guide future efforts at identifying SZSPD/AD comorbidities, both in clinical settings and for future studies.

However, there was evidence of significant heterogeneity between studies for every AD, and the overall rates should, thus, be considered with caution, keeping in mind that several factors contribute to modulate these rates.

In addition, the main limitation of this study is that meta-analytic approaches are dependent on the information available from the studies meeting the inclusion criteria. Hence, the impact of some variables (eg, gender, scope of diagnoses included) could not be explored as well as if these data had been reported within study. Moreover, as mentioned above, our analyses of potential moderators between studies could not address simultaneously several methodological features.

Furthermore, due to the exploratory nature of our analyses of the effect of potential moderator variables between studies, we did not correct the statistical threshold for multiple testing. For this reason, and because the different variables were not fully independent (eg, the 2 systematic studies of AGO, SP, SPP, and GAD rates both suspended the hierarchy rules), further studies targeting the effect of those variables on AD rates in SZSPD would be commended.

Conclusion

This meta-analysis confirms that AD are highly prevalent in SZSPD and that prevalence rates are higher than those reported for the general population but also highlights the great variations in rates between studies. Because identifying and treating these comorbid disorders can be clinically significant, our analysis of the sampling factors that affect these AD rates contributed to highlighting some risk factors for such co-occurrence. In addition, the observed effects for the variables related to diagnosis could help to improve detection of AD in SZSPD in

the future. The prognostic importance and the potential to delineate SZ subtypes or SZ dimensions should also be considered.

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Appendix

List of All Studies Included in the Meta-Analysis

1. Ulas H, Alptekin K, Akdede BB, et al. Panic symptoms in schizophrenia: comorbidity and clinical correlates. *Psychiatry Clin Neurosci.* 2007;61:678–680.
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