

Assessing and reporting the adverse effects of antipsychotic medication:
A systematic review of clinical studies, and prospective, retrospective,
and cross-sectional research

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Abstract

Objective: Adverse effects (AEs) of antipsychotic medication have important implications for patients and prescribers in terms of wellbeing, treatment adherence and quality of life. This review summarises strategies for collecting and reporting AE data across a representative literature sample to ascertain their rigour and comprehensiveness.

Methods: A PsycINFO search, following PRISMA Statement guidelines, was conducted in English-language journals (1980–July 2014) using the following search string: (antipsychotic* OR neuroleptic*) AND (subjective effect OR subjective experience OR subjective response OR subjective mental alterations OR subjective tolerability OR subjective wellbeing OR patient perspective OR self-rated effects OR adverse effects OR side-effects). Of 7,825 articles, 384 were retained that reported quantified results for AEs of typical or atypical antipsychotics amongst transdiagnostic adult, adolescent, and child populations. Information extracted included: types of AEs reported; how AEs were assessed; assessment duration; assessment of the global impact of antipsychotic consumption on wellbeing; and conflict of interest due to industry sponsorship.

Results: Neurological, metabolic, and sedation-related cognitive effects were reported most systematically relative to affective, anticholinergic, autonomic, cutaneous, hormonal, miscellaneous, and non-sedative cognitive effects. The impact of AEs on patient wellbeing was poorly assessed. Cross-sectional and prospective research designs yielded more comprehensive data about AE severity and prevalence than clinical or observational retrospective studies.

Conclusions: AE detection and classification can be improved through the use of standardised assessment instruments and consideration of subjective patient impact. Observational research can supplement information from clinical trials to improve the ecological validity of AE data.

Key words: Antipsychotic drugs; adverse effects; patient-centred research; subjective effects of drugs

Assessing and reporting the adverse effects of antipsychotic medication: A systematic review of clinical studies, and prospective, retrospective, and cross-sectional research

Antipsychotic medication is associated with numerous adverse effects (AEs), ranging from mild and intermittent (e.g., dizziness and nausea) to incapacitating (e.g., extrapyramidal symptoms: EPS), some of which can disrupt an array of physical and psychological systems.¹⁻³ Since the institution of antipsychotics in the 1950s, it has been recognised that patients generate subjective interpretations of the sensations that attend drug consumption. However, the imperative for standardising psychiatric phenomena arguably led “to a gradual disregard of subjective experiences... which were relegated to ‘soft’ science.”^{4: p.55} Correspondingly, much research has prioritized efficacy and safety parameters rather than the more subjective construct of tolerability. Interest in the latter was advanced by the work of Hogan et al.⁵ whose scale for assessing antipsychotic responses indicated that “maximum variability... is accounted for by items reflecting how the patient feels on medication, rather than what he knows or believes about medication” (p.177). In this respect patient testimony indicates that AEs are sometimes experienced as equally⁶ or more⁷ distressing than the symptoms targeted by the drugs.

The realization that AEs have implications for treatment adherence,⁸ quality of life,⁹ mortality,¹⁰ suicidal ideation,¹¹ and litigation suits¹² means greater attention is being paid to phenomenological aspects of AP use. The development of psychometrically robust scales that patients can reliably complete has also advanced the research agenda.¹³⁻¹⁵ This is important progress, given the necessity of auditing the relative prevalence and severity of AEs, and corresponding impact on patient wellbeing. In this respect, the substantial differences in AE profiles for different

antipsychotics (compared to robust, yet small, mean differences in efficacy)¹⁶ makes the former an important component of prescribing choices and, in accordance with best-practice guidelines, can empower service-users in making informed treatment decisions¹⁷ about the short- and long-term risk/benefit ratios.

Despite the utility of assessing and documenting AEs, recording is frequently deficient.¹⁸⁻²⁰ For example, an analysis of 182 randomised trials for assorted psychiatric interventions reported that 58.3% assigned more page space to authors' names and affiliations than safety statistics.²¹ A review of safety and tolerability data from 167 antipsychotic trials likewise indicated numerous failings, primarily inconsistent measurement and inadequate or confusing reporting.²² Other authors have provided detailed information on global AE domains (e.g. EPS²³), specific experiences (e.g. hyperprolactinaemia²⁴), or the safety and tolerability profiles for particular classes (e.g. long-acting injections²⁵) or brands²⁶ of drug. However, there is currently a lack of comprehensive information about the methods employed for assessing adverse antipsychotic effects across the broader evidence base (including, but not limited to, clinical trials), the types of effects being reported, and whether screening procedures differ according to the effects being assessed.

Aims of the Study

The aim of the current review was twofold: (1) to summarise strategies employed across a representative literature sample for obtaining and reporting data on the adverse effects of antipsychotic medication, and (2) to ascertain the comprehensiveness and methodological rigour of these strategies. As our approach was an exploratory one, we had no pre-specified hypotheses.

Materials and Methods

Search Procedure

The search, extraction, and data synthesis process were informed by PRISMA Statement guidelines.²⁷ Articles were searched for using the PsycINFO database (OVID interface) and employed the following search string: (antipsychotic* OR neuroleptic*) AND (subjective effect OR subjective experience OR subjective response OR subjective mental alterations OR subjective tolerability OR subjective wellbeing OR patient perspective OR self-rated effects OR adverse effects OR side-effects). This strategy resulted in 7,825 titles and abstracts.

Inclusion criteria

Studies were sought that appeared in peer-reviewed English-language journals from 1980 to July 2014 and reported quantified results for AEs of typical or atypical antipsychotics amongst transdiagnostic adult, adolescent, and child populations.

Exclusion criteria

Case studies/series, review articles, and conference proceedings were not retained. Also excluded were studies evaluating psychotropic medication without reporting specific findings for antipsychotics; studies only providing laboratory safety data; studies on healthy volunteers or non-psychiatric patient populations; studies reporting patient attitudes towards, beliefs about, and/or general wellbeing in relation to antipsychotic therapy without describing specific AE outcomes; studies reporting a single aspect (e.g., amenorrhea only) or domain (e.g., EPS only) of AEs; reports of augmenting antipsychotics with agents for controlling EPS; studies evaluating adjunctive therapies for antipsychotics as a primary outcome measure; studies

evaluating un-marketed or discontinued compounds. Studies only reporting a single global score from assessment instruments were also excluded, as it was not possible to code such studies according to separate AE domains.

Data Extraction

Information extracted from source papers included: date, research design, clinical population, participants' mean age, and whether medication dosage and polypharmacy was reported. For clinical studies, data was extracted on whether the number of participants withdrawing due to AEs was reported, and if so, whether the type(s) of effect leading to discontinuation were identified.

In order to derive a global score for the comprehensiveness of AE reporting in each study, the following information was extracted and coded as primary outcomes of interest:

Adverse effect assessment

For the purposes of the review, AEs were defined as secondary effects that are generally unwanted, are distinct from the medication's therapeutic effect, are not necessary for its desired action, and can be experienced and identified by patients independent of laboratory or clinical testing.²⁸⁻²⁹ Because the review was concerned with known effects of antipsychotics at normal doses, data on adverse drug *events* were not retained (e.g. overdose, instances of prescribing/dispensing malpractice).

Coding was organised according to the AE categories outlined in Table 1. For each domain, studies were coded 0 if no attempt was made to assess these effects, or if they were assessed but not reported. Assessment based on spontaneous self-report, observational monitoring, or unspecified checklists were coded as 1. Studies scored 2

if effects had been assessed using validated self-report inventories or structured clinical interviews. Metabolic effects were also coded as 2 if investigators provided numericised results pertaining to weight gain. Because the review was not assessing *AE prevalence*, studies still scored for a particular domain if no participants reported it, but the authors specified an intention to assess it (i.e., included a scale with relevant items) and/or commented on its absence.

--Table 1 here--

Assessment of global impact

In addition to quantifying AEs, clinical utility is enhanced if research addresses the broader impact of antipsychotic consumption on patient wellbeing. Studies that did not assess this, provided generalised anecdotal statements (e.g., “side-effects were mostly mild and transient”), or only addressed impact of pre-selected effects, such as EPS, were coded 0. Studies that quantified responses using non-standardised questionnaires (e.g., authors’ own checklist), or employed a known severity scale (e.g., mild, moderate, severe) across all domains of AEs were coded with 1. Studies assessing the subjective experience of antipsychotic usage using validated instruments (e.g. the Subjective Well-being Under Neuroleptics scale [SWN]¹³) or used AEs as predictors/covariates of validated outcomes (e.g., Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q³⁰]) were coded with 2.

Timeframe

Short-term assessment cannot provide comprehensive data on AEs with long induction periods (e.g. weight gain, sexual dysfunctions, amenorrhoea, tardive

dyskinesia). Assessment length was therefore coded as: 0= \leq 12 weeks; 1= 13–24 weeks; 2= \geq 25 weeks. If treatment duration was not provided, then timeframe was coded according to the length of the study. For cross-sectional studies, coding was organized according to whether authors reported mean treatment duration.

Sample size

Larger samples have greater representation, as well as permitting identification of less common effects. Because no clear guidelines exist for determining adequate population size for antipsychotic AEs, studies were partitioned and coded according to the second, third and fourth percentile of the entire sample: 0= \leq 76 (49.2%; n=189); 1= 77 (26.3%; n=101); 2= \leq 225 (24.2%; n=93).

Conflict of interest

Research subsidised by pharmaceutical companies has been shown to be more likely to support industry interests,³¹⁻³² including incomplete or inconsistent AE reporting,³³ or reporting more favourable AE results for the sponsor's product relative to independent trials.³⁴ Studies receiving industry funding, or in which authors declared receipt of honoraria from drug companies, were therefore coded with 0. Those with no reported affiliation were coded with 1.

Global Comprehensiveness Score

This was calculated by summing scores for each AE domain (0-18), global impact (0-2), timeframe (0-2), sample size (0-2), and conflict of interest (0-1), resulting in a maximum possible score of 25 (see Table 2).

Analysis

Variables related to study characteristics and comprehensiveness criteria were summarised using descriptive statistics. Non-parametric analyses (between-group comparisons for the assessment of AEs, global impact, and declared conflict of interest) were performed with the Kruskal-Wallis H test, Dunn's multiple comparison post-hoc test, and Friedman's two-way analysis of variance by ranks. Parametric analyses (timeframe, global comprehensiveness scores) were conducted using one-way ANOVA procedures and the Tamhane *T2* post-hoc comparison. Associations between variables were computed with Spearman's rank correlation coefficient. All analyses used SPSS Statistics v.21.0 software.

Reliability checking

Data were extracted and coded by the first author and entered into an electronic data collection form, which was subsequently re-checked for missing or incorrect entries. Data deemed ambiguous were discussed and categorised in consultation with the second author, with any discrepancies resolved by consensus. Rating was not blinded to author or results.

As a reliability measure, 16 articles were randomly selected and coded by an independent rater. Values were compared and inter-rater reliability calculated using Cohen's κ . Of the 13 categories, seven showed 100% agreement, five 93.8% agreement ($\kappa = .88$), and one 87.5% agreement ($\kappa = .76$). Using Landis and Koch's³⁵ guidelines, in which a κ value of $>.70$ suggests strong concordance, all variables indicated good reliability.

Results

Of the recovered publications, 819 fulfilled criteria on the basis of title and abstract review and were retrieved to assess inclusion eligibility. Three articles could not be located. Of the remaining papers, 384 met criteria and were retained for review. These were subsequently organised according to four research designs: retrospective observational (n=40), prospective observational (n=50), cross-sectional (n=67), and clinical intervention (n=227).

Sample characteristics are presented in Table 2. The most common population was psychosis patients (222; 57.8%), followed by developmental disorders (30; 7.8%) and bipolar disorder (25; 6.5%). The majority of studies recruited adults (259; 67.45%), with a smaller number reporting results from child/adolescent samples (66; 17.2%), elderly participants (32; 8.3%), or mixed age groups (27; 7.0%). Medication dosage was reported in 331 studies (86.2%) and polypharmacy in 323 (84.1%).

--Table 2 here--

Assessment of Adverse Effects

The review identified 37 instruments for assessing AEs. Table 3 presents the 10 most commonly used. Figure 1 displays the percentage of studies from each design reporting on different AEs and Figure 2 presents the percentage of studies across the whole sample using informal or standardised measures for each AE category.

EPS were the most consistently assessed and reported in the sense they were most likely to be referred to, and more likely to be assessed using validated scales. This was closely followed by cognitive effects, although in many cases this was limited to only sedation/fatigue. When frequencies were re-calculated to determine the proportion of studies reporting at least one non-sedative cognitive effect using

either standardised or informal measures there was a noticeable decrease: 10 retrospective observational studies (25.0%), 38 prospective observational (76.0%), 50 cross-sectional studies (74.6%), and 134 clinical studies (59.0%). As a weighted mean percentage across all four designs, this translated to a decrease from 90.7% to 60.4%. Of the remaining categories, metabolic and autonomic effects were reported in around two thirds of papers. Approximately half reported miscellaneous 'other', anticholinergic, and hormonal effects. Affective and cutaneous effects had the poorest measurement, being assessed or reported in less than a third of cases.

The 0-2 coding frame was used to calculate a mean rank score of methodological rigour for each AE category. Results were: EPS (7.15), metabolic (6.47), cognitive (6.14), autonomic (5.17), anticholinergic (4.57), 'other' (4.69), hormonal (4.12), affective (3.48), and cutaneous (3.20). Comparisons, using Friedman's two-way analysis of variance, indicated that EPS scored significantly higher than all other categories (all p 's = .001). There was no significant difference between metabolic and cognitive effects, or affective and cutaneous effects (all p 's = 1.00). Hormonal effects did not differ significantly from anticholinergic or 'other' effects, and anticholinergic effects did not differ significantly from 'other' or autonomic effects (all p 's \geq .086). Each of the remaining pairwise comparisons were significant (all p 's = .001).

When examining mean ranks for AEs according to study design, the Kruskal-Wallis H statistic was not significant for autonomic effects, or 'other' miscellaneous effects (all p 's \geq .117). Of the remaining effects, post-hoc comparisons indicated that EPS were best assessed in clinical and cross-sectional designs (all p 's = .001), and metabolic effects were best assessed in clinical studies and observational prospective designs (all p 's = .001). Cutaneous (all p 's \leq .02) and anticholinergic effects (all p 's \leq

.034) were best assessed in cross-sectional studies. Cognitive, affective, and hormonal effects had the best assessment in both cross-sectional and observational prospective designs (all p 's \leq .024).

--Table 3 here--

--Figure 1 here--

--Figure 2 here--

Assessment of Global Impact

Table 4 presents the measures identified in the review for assessing global impact of antipsychotic use. This was poorly addressed across the literature, with only 59 studies (15.4%) employing a validated instrument to report patient experiences. Of these, seven did not employ the scales presented in Table 4 but calculated associations between AEs and standardised outcomes like the Q-LES-Q. A further 75 (19.5%) did not employ validated measures, but quantified AE impact with more informal criteria (e.g., mild/moderate/severe ratings).

The study designs significantly differed in assessment of global impact ($\chi^2(3)=121.83, p=.001$). Post-hoc comparisons indicated that mean rank scores for cross-sectional studies were significantly higher than the other three designs (all p 's = .001), with observational prospective studies scoring higher than observational retrospective and clinical studies ($p=.001$). There was no significant difference between observational retrospective and clinical studies ($p=.27$).

Withdrawal from clinical studies

Data was additionally extracted for the number of clinical studies reporting how many participants withdrew due to AEs. Across the sample, only 20 (8.8%) did not address the issue of drug tolerability on discontinuation rates. Of the remaining 207, 50 (22.02%) reported no drop-outs; 80 (38.6%) provided the number of withdrawals; and 73 (35.3%) reported the numbers of withdrawals and additionally specified the types of effects leading to it.

--Table 4 here--

Timeframe

Across the entire sample, the mean (SD) timeframe for antipsychotic usage was 40.7 weeks (90.6). Cross-sectional studies had the highest mean timeframe at 104.2 weeks (171.1), followed by prospective observational studies at 63.7 weeks (115.2), retrospective observational at 58.7 weeks (83.6), and clinical studies at 23.1 weeks (55.3). This distribution was significantly different across study designs ($F(3)=11.10$; $p=.001$). Post-hoc tests indicated that clinical studies reported significantly shorter durations than cross-sectional studies ($p=.045$). No other pairwise comparisons showed significant differences. It should also be noted that the cross-sectional studies had a large amount of missing or unusable data (46.3%; 31/67). This was due to authors either not specifying the duration of participants' antipsychotic use, or reporting a broad range without providing a mean figure.

Sample size

Across all studies, the mean (SD) sample size was 576.2 (3336.6). Mean sample sizes according to study design are presented in Table 2, of which the largest was

prospective observational studies, followed by retrospective observational studies, cross-sectional studies, and clinical studies. Although there was significant variation across the sample ($F(3)=7.4$; $p=.001$), post-hoc tests did not reveal any differences between designs (all p 's $\geq .23$).

Conflict of Interest

The design with the greatest frequency of drug company affiliations were clinical studies (70.0%; 159/227), followed by prospective observational (38.0%; 19/50), cross-sectional (23.9%; 16/67), and retrospective observational (17.5%; 7/40). This difference in distribution was significant ($\chi^2(3)=73.67$, $p=.001$), with clinical studies reporting significantly more conflicts of interest than each of the other three designs (all p 's = .001). No other pairwise comparisons were significant.

Global Comprehensiveness Rating

There was a weak positive association between publication date and total comprehensiveness score across the entire sample, indicating that AE assessment and reporting has improved marginally over time ($r_s = .18$, $p=.001$).

There was a significant difference in scores across the four study designs ($F(3)=27.39$; $p=.001$). Post-hoc tests indicated no differences between cross-sectional and prospective observational studies ($p=.08$). However both these designs scored significantly higher than clinical studies and retrospective observational studies (all p 's $\leq .01$). In turn, clinical studies scored significantly higher than retrospective observational research ($p=.001$).

A *post-hoc* analysis was also performed to examine comprehensiveness score according to sample age group: adults aged ≥ 66 years ($n=32$), adults aged 18-65

years (n=259), and children/adolescents aged ≤ 17 years (n=66). Twenty seven studies were excluded from this analysis, either because mean age was not provided (n=11) or because the authors had recruited mixed samples of children/adolescents and adults (n=16). There was a significant difference across the sample ($F(2)=218.70$; $p= .001$). The mean (SD) score of 6.88 (3.07) for elderly adults was significantly lower than the mean of 10.77 (4.57) for adults aged 18-65, or the mean of 10.02 (3.67) for child/adolescent samples (all p 's = .001). There was no significant difference between adult and child/adolescent samples ($p= .41$).

Discussion

Accurate detection, classification and management of AEs is important from both clinical and research stances. This review systematically examined strategies used to record and report antipsychotic AEs, and assessed the clarity and comprehensiveness of these. Firstly, the results demonstrate that neurological, metabolic, and sedation-related cognitive effects are most consistently assessed and reported across the literature. Secondly, the global impact of antipsychotics on patient wellbeing was poorly assessed. Finally, the cross-sectional and prospective research designs yielded the most comprehensive AE data.

Assessment of Adverse Effects

The current findings are similar to Pope et al.²² whose review of 167 antipsychotic trials likewise found that EPS were assessed more frequently and systematically than other AEs. Given their debilitating and potentially irreversible nature, it is encouraging that motor disturbances were carefully reported across different designs. Nevertheless, the reduced risk of EPS associated with atypical antipsychotics means

privileging their assessment over other effects may no longer be clinically justified. This inconsistent assessment of non-neurological effects replicates the conclusions of existing surveys,^{22,50-51} despite concerns about the substantial impact of non-neurological AEs on factors like physical attractiveness,⁵² feelings of reduced intelligence and creativity,⁵³ and social stigma and ridicule.⁵⁴ Furthermore, while sedation was generally well-reported, affective and non-sedative cognitive AEs were referred to far less frequently, despite patient testimony that subjective effects like dysphoria (e.g., feeling ‘robotic’, ‘emotionally empty,’⁵³) are both common and distressing.

In addition to the types of AEs reported, limitations were also apparent in their assessment. An exception to this was EPS. For example, a review of 2000 intervention studies between 1950 and 1998, 59% of which were for antipsychotics,⁵⁵ found only 17% employed either the SAS, AIMS or ESRS to assess neurological AEs. The current findings indicate a welcome reverse in this trend. However, non-neurological AEs were much less likely to be assessed with validated measures. This is important because solicited, systematic inquiry using structured checklists is more likely to provide comprehensive data than open-ended questioning, which in turn is more efficient than spontaneous/voluntary reporting. Although the latter has the advantage of simplifying research protocols by reducing the number of formal measures participants need to complete, as well as identifying AEs that patients deem most relevant, there is a clear rationale for not relying on these methods alone. For example, Yusufi et al.⁵⁶ found that memory and concentration problems were respectively reported by 0% and 0.1% of their participants under open-ended questioning, compared to 37% (38/103) and 38% (39/103) using a validated checklist. In turn, successful AE screening approximately doubles when spontaneous self-report

is supplemented with rating scales.⁵⁷⁻⁵⁸ Neither is this limited to severe effects, with the detection of mild to moderate problems necessitating a change in clinical management improving by approximately 40% using systematic checklists compared to open-ended inquiry.⁵⁹

It is important that research inconsistencies do not translate into mistaken assumptions about prevalence in clinical practice, and the privileging (for example) of enquiries about EPS, weight gain, and sedation over other domains. For example, although affective and cutaneous effects were infrequently assessed or reported across the sample these experiences have prevalence rates of between 38.4–66.0% (emotional) and 29.2–50.0% (cutaneous).⁶⁰⁻⁶³ Similarly, a probability sample of 243 patients found higher rates of emotional (18.8%) and cutaneous (17.3%) effects than EPS such as body rigidity (11.4%) and tardive dyskinesia (7.6%; although not akathisia: 27.1%).⁶⁴

Further limitations in reporting and interpretation of AE data reflected those previously observed in existing reviews of antipsychotic trials^{22,65-67} as well as other medical disciplines.²⁰⁻²¹ These included timeframes that were insufficient to detect AEs with long induction periods, inadequate detail about AE frequency/duration, reporting aggregated subscale scores from different measures rather than specifying individual effects, not reporting numericised results of Likert-scale severity measures and/or using ambiguous severity summaries (e.g., ‘the majority of patients were not troubled by AEs’; ‘AEs were mild and transient’) without providing operational definitions of what these terms imply. Inconsistent terminology and classification was also evident (e.g., ‘agitation’ without denoting cognitive AEs, psychiatric distress, or the neurological impact of akathisia; differentially classifying seizures as a form of EPS, an autonomic effect, or an unspecified ‘other’ effect). In this respect, The

Coding Symbols for Thesaurus of Adverse Reaction Terms⁶⁸ was instigated to support standardised and consistent reporting. However of the 362 papers in the review published from 1991, only 19 referred to these guidelines. Only three cited the more recent Medical Dictionary for Regulatory Activities⁶⁹ terminology.

Specific limitations in the design of clinical studies included the use of first-generation agents as comparators (which is likely to inflate EPS incidence data), only reporting AEs noted in at least 10% of patients or those that significantly differed between test and comparator drugs, not providing follow-up on withdrawn participants, and not clearly specifying whether cognitive/affective changes were the results of medication or underlying psychiatric states. Carry-over effects were also inconsistently addressed (e.g., if patients have gained weight from prior medication, weight gain may be underestimated as the potential for further increase is limited⁷⁰). There was also a tendency to report AEs in ways which have negligible clinical meaning: for example, reporting sample-wide mean changes in weight, EPS scales, and plasma prolactin elevation as opposed to the absolute proportions of participants gaining weight, the number of patients reaching diagnostic threshold for movement disorders, or those exhibiting hyperprolactinaemia.

Assessment of Global Impact

Withdrawal rates due to AEs were reported consistently amongst the clinical studies, although there was negligible transparency about the types of effects precipitating drop-out. While separate reporting of tolerability and efficacy as reasons for premature discontinuation is encouraging, this failure to specify the AEs impairs the consistency and expediency of the measure, particularly if efficacy-related events (e.g., worsening of psychosis) are included in the AE category.⁶⁷ Furthermore, most

studies prioritised quantifying AEs over establishing their subjective impact. Even with our lenient criteria (e.g. coding for Likert-style mild/moderate/severe indicators) only 34.9% of studies scored on this measure. Validated scales assessing subjective tolerability were particularly poorly utilised, being reported in only 15.6% of cases. This absence is of especial concern, given that subjective wellbeing on antipsychotics is identified as a major component by the Remission in Schizophrenia Working Group.⁷¹

Distress from AEs “is a moving target, affected by social expectations, knowledge, and alternative choices” wherein objective measures of particular effects will not inevitably correlate with subjective impact.^{58: p.46} For example, distress may fluctuate according to the respite drugs provide from symptoms.⁷² Other variables influencing treatment satisfaction can include the quality of the therapeutic alliance,⁷³ shared decision-making in care planning,⁷⁴ and frequency of hospital admissions.⁷⁵ Additional variations may be gender specific, with women more likely to be distressed by weight gain and men more likely to experience distress over sexual dysfunction.⁷⁶ Taken together, the current results emphasise the importance of more proactive strategies for assessing the impact of antipsychotic consumption. For example, Naber¹³ conceptualises the global effects of antipsychotics within a five-factor model of mental functioning, physical functioning, emotional regulation, self-control, and social integration; subsequently expanded to include the influencing factors of psychopathology and symptomatic improvement, psychosocial factors, phase and severity of illness, attitudes toward pharmacological treatment and insight, and physical AEs and associated distress.⁷⁷ Studies operationalising these constructs with the SWN¹³ scale report significant associations with drug compliance,^{13,78} with stronger correlations between SWN factors and depression and anxiety than SWN

factors and psychotic symptoms themselves.⁴⁴ Our finding that AE assessment and reporting was significantly less rigorous in elderly populations additionally highlights the need for increased vigilance amongst patients for whom experiences like dementia and negative symptoms makes spontaneous reporting of distress more problematic. In summary, AEs should not be minimised as an inevitable penalty of successful treatment. Vigilant approaches to detection can facilitate prompt identification of difficulties, instigation of interventions to minimise patient burden, and ultimately reduce the likelihood that therapeutic impact becomes overridden by AEs.

Research Designs

Levine⁷⁹ defines three methodological considerations for improving AE data: assessment method, timeframe, and whether information permits judgments about cause and extent of clinical impact. This closely corresponds to our own aggregated coding for comprehensiveness, on which basis prospective observational and cross-sectional designs emerged as the most comprehensive data sources. This was particularly owing to their larger sample sizes, greater use of standardised assessment, and consideration of both global drug impact and long-term antipsychotic use.

Notwithstanding the considerable advantages of clinical trials for minimising bias and confounding, and for generating valuable data against placebo or comparator drugs, we found that AE reporting was often limited by small samples, short assessment durations with limited generalisability, an over-reliance on spontaneous self-report data, and the tendency to emphasise efficacy and symptom control over tolerability. Retrospective studies (which in the current review mostly encompassed medical note audits) can in turn generate insights into large samples of ‘real-world’ patients and practice, whilst remaining limited by unsystematic assessment and incomplete data.

Nevertheless, it is also important to acknowledge that all research designs carry relative strengths and limitations, and that the most comprehensive insights into AEs can probably be reached by considering heterogeneous evidence sources together.⁶⁵ For example, cross-sectional studies are less likely to define the nature of the intervention and have fewer contingencies to control confounding. Similarly, despite the limitations of spontaneous self-report, this method has a capacity to elicit rare or unexpected effects that is prohibited with standardised scales. Nevertheless, our findings suggest that despite the primacy placed on clinical trials, observational studies are also a useful source of data for policy makers, clinicians and researchers seeking to understand AE prevalence and impact.

Limitations

The intention of this review was to characterise recurring themes and limitations in the antipsychotic literature. In this regard its main strength – a comparatively large, representative sample – was also the source of its main limitations. The inclusion of so many publications necessitated summarising a sizeable literature via broad conclusions. Some nuances of individual studies were not captured. Furthermore, our review was not pre-registered.

Our AE coding may have reduced discriminative capacity by subsuming diverse experiences under a single domain (e.g., sexual dysfunctions, menstrual irregularities, and gynaecomastia were all categorised as ‘hormonal’). Similarly, inconsistent classification in the sampled studies meant reported results did not always correspond with our categories. For example, some authors used ‘other effects’ to refer to all non-neurological AEs. For subjective psychological effects, it was not always clear to what extent these were the result of psychosis/psychosocial

adversity rather than medication; as such the review may have over-estimated assessment rates of cognitive and emotional AEs.

Search limitations may also have created bias. This includes our decision, because of the large size of the literature, to limit our search to a single database. Whilst our choice of PsycINFO increased the likelihood of detecting the type of observational, non-clinical studies in which we were interested, reliability would have been improved by including other databases. Similarly, the lack of double extraction procedures may have reduced the quality of our findings. The exclusion of non-English language journals further risked language bias. The latter may be particularly relevant, as cross-cultural disparities are apparent in AE identification⁸⁰ and reporting.⁸¹⁻⁸² Demonstrated inadequacies in the ways AE data is indexed in electronic databases⁸³ means relevant studies may have been missed. It is further possible that studies with low scores for AE assessment (e.g., small samples and reliant on spontaneous self-report) simply reflected a genuine absence of particular effects. In this respect the comprehensiveness scores were also subjectively operationalised. However the high inter-rater reliability, as well as consistency of the results with both existing literature, and between and within the four study designs, suggests the findings retain reasonably strong validity.

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Table 1. Common adverse effects of antipsychotics categorised according to physiological systems.

| Effect domain | Descriptor | Examples |
|-----------------|--|---|
| Affective | Emotional disturbances | Depression, anhedonia, dysphoria, affective flattening, problems with emotional regulation |
| Anticholinergic | Neuromuscular inhibitions resulting from disturbance to acetylcholine receptors in the central and peripheral nervous system | Dry mouth, constipation, difficulty urinating, increased need to urinate, blurred vision |
| Autonomic | Specific influences on the autonomic nervous system | Dizziness, nausea, increased perspiration, diarrhoea, heart palpitations/tachycardia |
| Cognitive | Impairment to cognitive faculties | Concentration difficulties, memory problems, anxiety and mental tension, sedation, insomnia, increased/decreased dreaming |
| Cutaneous | Hypersensitive dermatological response | Skin rash or itchiness, dry skin, photosensitivity, acne, psoriasis, skin pigmentation/discolouration |
| EPS | Movement disorders resulting from blockade of dopamine receptor in the basal ganglia | Acute dystonia, akathisia, akinesia, bradykinesia, dyskinesia, tremors, rigidity |

| | | |
|-----------|---|---|
| Hormonal | Sexual and somatic disturbances induced by elevated levels of the peptide hormone prolactin | Amenorrhoea, anorgasmia, increased/diminished sex drive, erectile/ejaculatory dysfunction, gynaecomastia, galactorrhoea |
| Metabolic | Interference with normal metabolism through activation of SMAD3 protein | Weight gain, polydipsia |
| Other | Additional non-specific side effects | Headaches, paraesthesia, nose bleeds |

Table 2. Main characteristics of the studies included in the review.

| Design | Clinical population | Sample age | Sample size | Medication reporting | Global comprehensiveness score ^a | |
|------------------------------------|---|---|--|--|---|--------------------------|
| | | 1. 11 ≤ 17 years 2. 18-65 years 3. ≥ 66 years 4. Mixed/ unspecified | M (SD) Range | 1.dosage 2.polypharmacy | M (SD) Range | |
| Retrospective observational (n=40) | 27 medical record audit 7 post-marketing surveillance/ pharmacovigilance data 5 retrospective evaluation 1 staff census | 18 transdiagnostic 10 psychosis 5 bipolar 3 dementia 1 PTSD 1 psychotic depression 1 mood disorders 1 delirium | 11 (27.50%) 17 (42.50%) 7 (17.50%) 5 (12.50%) | 1118.85 (3627.30) 10 – 20592 | 33 (82.50%) 33 (82.50%) | 7.70 (2.23) 4–13 |
| Prospective observational (n=50) | | 36 psychosis 9 transdiagnostic 2 DD 3 dementia | 5 (10.0%) 39 (78.0%) 3 (6.0%) 3 (6.0%) | 2459.66 (8412.72) 10– 56861 | 41 (82.0%) 39 (78.0%) | 11.48 (4.14) 3–21 |

| | | | | | | |
|---|---------------------------------|-----------------------|--------------|-----------------|--------------|--------------|
| Cross-sectional (n=67) | | 49 psychosis | 1 (1.49%) | 286.49 (507.18) | 32 (47.76%) | 13.75 (5.74) |
| | | 8 unspecified | 61 (91.04%) | | 39 (58.21%) | |
| | | 7 transdiagnostic | 0 | 8 – 2399 | | 5–24 |
| | | 3 DD | 5 (7.46%) | | | |
| Clinical trial/ intervention studies (n=227) | 89 open-label uncontrolled | 127 psychosis | 49 (21.59%) | 153.05 (294.61) | 225 (99.12%) | 9.43 (3.54) |
| | 47 RCT double-blind | 20 bipolar | 142 (62.56%) | | 212 (93.39%) | |
| | placebo- controlled | 25 DD | 24 (10.57%) | 6 – 2585 | | 2–22 |
| | 58 RCT double-blind | 14 dementia | 12 (5.29%) | | | |
| | 15 RCT open-label | 6 TS | | | | |
| | 11 RCT single-blind | 6 transdiagnostic | | | | |
| | 6 open-label comparison | 4 anxiety | | | | |
| | 1 single-blind, uncontrolled | 4 BPD | | | | |
| | | 21 other ^b | | | | |
| | | | | | | |

Note. BPD = borderline personality disorder; DD = developmental disorders; PTSD = posttraumatic stress disorder; TS = Tourette's syndrome

^a Maximum possible score: 25; ^b 3 conduct disorder; 3 delirium; 3 depression; 2 eating disorders; 2 prodromal psychosis; 2 PTSD; 2 BPD; 1 cocaine dependence; 1 drug-induced psychosis; 1 obsessive compulsive disorder; 1 somatoform disorders

Table 3. The ten most frequently used measurement scales identified in the review for assessing adverse effects of antipsychotic medication.

| Instrument | Description of content | Use across the sample (n=384) | Assessment domains | |
|---|--|-------------------------------|--------------------|-------------------|
| | | | EPS only | Multi-dimensional |
| <i>Simpson–Angus Extrapyrarnidal Signs Scale (SAS)³⁶</i> | 10 items (gait, arm dropping, shoulder/elbow/wrist rigidity, head rotation, glabella tap, tremor, salivation, akathisia); clinician-rated 5-point Likert scale | 116 (30.21%) | X | |
| <i>Abnormal Involuntary Movement Scale (AIMS)³⁷</i> | 12 items; 4 subscales (orofacial, extremity and truncal tardive dyskinesia; condition of teeth /dentures); clinician-rated 4-point Likert scale | 104 (27.08%) | X | |
| <i>Barnes Akathisia Rating Scale (BARS)³⁸</i> | 4 items (objective assessment, subjective awareness, subjective distress, global clinical assessment); clinician and self-rated 5-point Likert scale | 85 (22.14%) | X | |
| <i>The Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)³</i> | 48 items; 3 subscales (autonomic, neurological, other); self-report 3-point Likert scale | 51 (13.28%) ^a | | X |
| <i>Extrapyrarnidal Symptoms Rating Scale (ESRS)³⁹</i> | 41 items; 4 subscales (Parkinsonism, dystonia, tardive dyskinesia, akathisia); self-report 5-point Likert scale | 35 (9.11%) | X | |
| <i>The Dosage Record Treatment Emergent Symptom Scale (DOTES)⁴⁰</i> | 28 items; 8 subscales (neurologic, cardiovascular, psychic, hepatic gastrointestinal, hematologic, urologic, other); structured interview and 4-point Likert scale | 15 (3.91%) | | X |

| | | | |
|---|---|------------|---|
| <i>Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS¹)</i> | 41 items; 7 subscales (extrapyramidal, psychic, anticholinergic, autonomic, cutaneous, hormonal, miscellaneous); self-report 5-point Likert scale | 14 (3.65%) | X |
| <i>Arzneimittelsicherheit in der Psychiatrie side effect rating scale (AMDP⁴¹)</i> | 47 items; 9 subscales (neurologic, psychic, cardiovascular, gastrointestinal, hepatic, cutaneous, urologic, hematologic, unspecific); clinician and self-rated 5-point Likert scale | 7 (1.82%) | X |
| <i>Drug-Induced Extrapyramidal Symptoms Scale (DIEPPS⁴²)</i> | 9 items (gait, bradykinesia, sialorrhea, rigidity, tremor, akathisia, dystonia, dyskinesia, global impact); 5-point clinician and self-rated Likert scale | 5 (1.30%) | X |
| <i>The St. Hans Rating Scale for Extrapyramidal Symptoms (SHRS⁴³)</i> | 18 items; 4 subscales (hyperkinesia, Parkinsonism, dystonia, akathisia); clinician-rated 6-point Likert scale | 6 (1.56%) | X |

Note. Some studies employed more than one instrument.

^a Two studies only used the neurological subscale; one study only used items for sexual dysfunction.

Table 4. Measurement scales identified in the review for assessing the global subjective impact of antipsychotic medication.

| Instrument | Description | Subscales | Abridged sample items | Use across the sample (n=384) |
|--|--|--|--|-------------------------------|
| <i>Drug Attitude Inventory (DAI⁵)</i> | 30 items; self-report dichotomous scale | Positive and negative experiences of medication; attitudes to health and illness; attitude to physicians, control issues, prevention and harm. | <i>I feel strange, 'doped up,' on medication</i> | 18 (4.70%) |
| | 10-item short version | | <i>For me, the good things about medication outweigh the bad</i> <i>I feel more normal on medication</i> | 9 (2.34%) |
| <i>Subjective Well-Being Under Neuroleptics scale (SWN)</i> | 38 items; self-report 6-point Likert scale ¹³ | Emotional regulation, self-control, mental functioning, social integration and physical functioning | <i>I feel very comfortable in my body</i> | 13 (3.40%) |
| | 20-item short version ⁴⁴ | | <i>I am full of energy and life</i> <i>I am imaginative and full of ideas</i> | 12 (3.13%) |
| <i>Subjects' Response to Antipsychotics questionnaire (SRA¹⁴)</i> | 74 items; self-report 3-point Likert scale | Recovery, diminished sociability, affective flattening, weight gain, sexual anhedonia, sedation, increased sleep, EPS | <i>Due to the antipsychotic medication I am more confident</i> <i>Due to the antipsychotic medication my creativity has lessened</i> <i>Due to the antipsychotic medication I have less drive to see a great many people</i> | 3 (0.78%) |
| <i>Medication Adherence Rating Scale (MARS⁴⁵)</i> | 10 items; self-report dichotomous scale | Subjective response and medication adherence | <i>I feel weird, like a 'zombie,' on medication</i> <i>It is unnatural for my mind and body to be controlled by medication</i> <i>My thoughts are clearer on medication</i> | 1 (0.26%) |

| | | | | |
|--|---|---|--|-----------|
| <i>Rating of Medication Influences Scale in Schizophrenia (ROMI⁴⁶)</i> | 20 items; self-report 3-point Likert scale | Reasons for medication compliance and non-compliance | <i>Are you willing to take your medication because you are pressured or forced to?</i> <i>Are you reluctant to take your medication because you feel embarrassed?</i> <i>Are you reluctant to take your medication because the side-effects...are too upsetting for you?</i> | 1 (0.26%) |
| <i>Reasons for Antipsychotic Discontinuation/Continuation (RAD-I⁴⁷)</i> | Open-ended interview including a 3-point Likert scale | Treatment benefits, adverse events, distal reasons other than direct medication effects | <i>Patient was unable to form a therapeutic alliance or make a connection with members of the treatment team</i> <i>Another person told the patient to stop taking the medication</i> <i>The patient experienced intolerable side effects</i> | 1 (0.26%) |
| <i>Satisfaction with Antipsychotic Medication Scale (SWAM⁴⁸)</i> | 33 items; self-report 5-point Likert scale | Treatment acceptability and medication insight | <i>Antipsychotic medication interfere with my everyday activities</i> <i>I find it unpleasant to take antipsychotic medication</i> <i>I tolerate the side-effects I get from my antipsychotic medication</i> | 1 (0.26%) |

Note. Some studies employed more than one instrument.

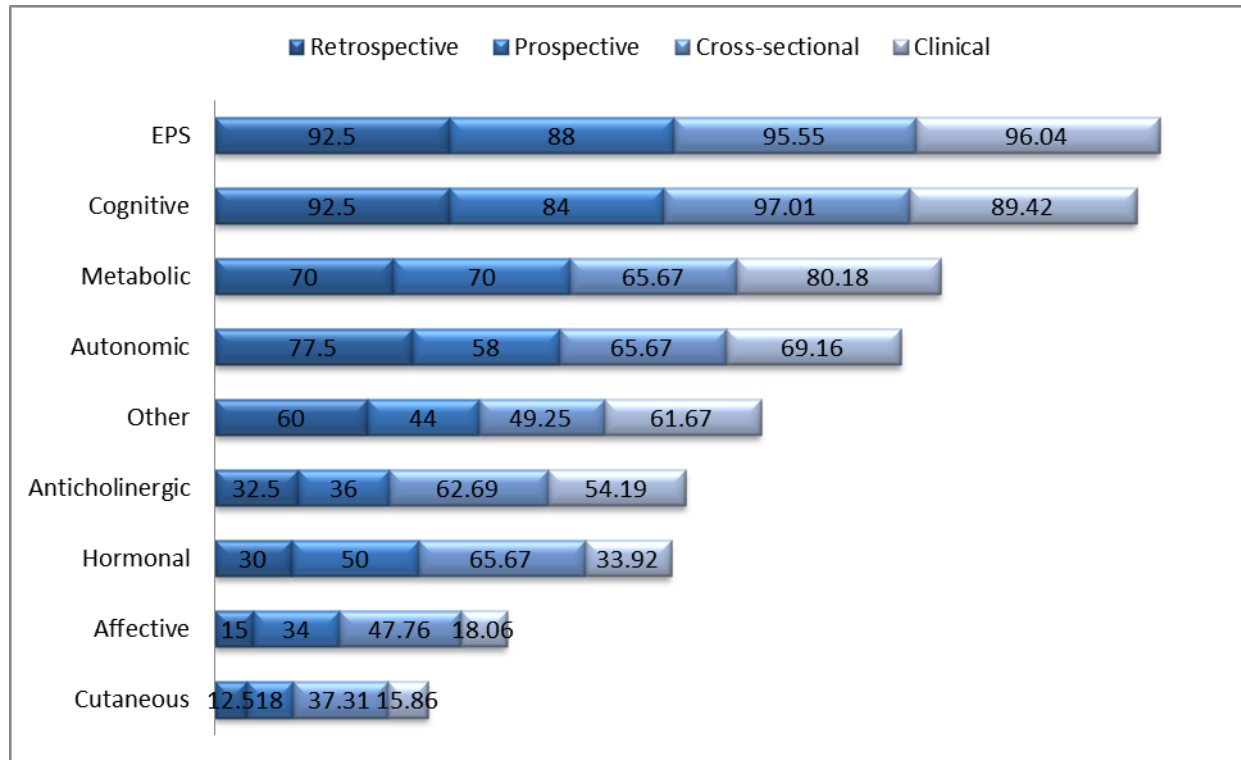


Figure 1. The percentage of studies from each design reporting on different types of antipsychotic adverse effects.

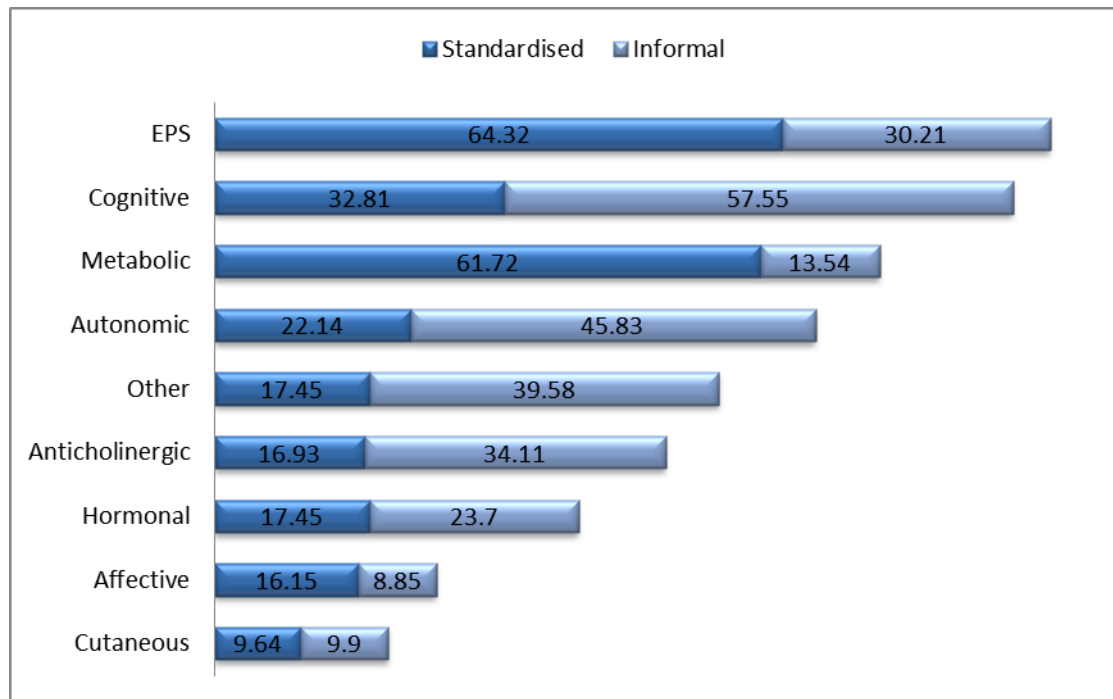


Figure 2. The percentage of studies in the sample reporting on antipsychotic adverse effects with either standardised or informal measures.