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Medication-Free Research in Early Episode Schizophrenia: Evidence of Long-Term Harm?

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This study investigates the question of whether short periods of medication-free research in early episode schizophrenia result in demonstrable long-term harm to human subjects. A meta-analysis of published quasi-experimental and random assignment studies that had a majority of first- or second-episode schizophrenia spectrum subjects, at least 1 initially unmedicated group, and a minimum of 1-year results was conducted. Only 6 studies, with 623 subjects, met inclusion criteria. The initially unmedicated groups showed a small, statistically nonsignificant long-term advantage ($r = -0.09$). Incorporating only random assignment studies into a composite effect size produced a similar near-zero result ($r = 0.01$). Good-quality evidence is inadequate to support a conclusion of long-term harm resulting from short-term postponement of medication in early episode schizophrenia research. A categorical prohibition against such research should be reconsidered.

Key words: psychosis/first episode/meta-analysis/spontaneous remission/subgroup/subtype

Introduction

The controversy in medicine sparked by Rothman and Michels'[1] article on the "continuing unethical use of placebo controls" extends into schizophrenia research in the debate over the ethics of medication-free periods.[2–4] Efforts to protect human subjects while simultaneously advancing scientific knowledge seek to integrate the ethical principle of not harming subjects through withholding a proven treatment[5] with the scientific advantages of placebo controls.[6] Tension inherent in these dual imperatives has led to considerable debate in the scientific literature,[7] to a National Placebo Initiative in Canada to reconsider conflicting placebo research policies,[8] and to several revisions in the Declaration of Helsinki.[9,10] The latest Helsinki revisions[10(p5)] have moved toward allowing placebo-controlled trials under carefully controlled conditions that include (1) "compelling and scientifically sound methodological reasons" and (2) that the "method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm." Carpenter and colleagues have reviewed the evolution of the Declaration of Helsinki and its application to medication-free research in schizophrenia, and they have suggested specific criteria for evaluating schizophrenia research proposals for compliance with the most recent ethical clarifications.[9]

In early episode schizophrenia research, the suggestion that postponing administration of antipsychotic medications may result in a poorer clinical course[11] has raised the parallel ethical consideration of whether there is harm to subjects through "deferring neuroleptic treatment in first-episode patients while studies are conducted."[12(p181)] In an influential article, "Neuroleptics and the Natural Course of Schizophrenia," Wyatt reanalyzed 22 mostly first-episode studies that compared antipsychotic medication with placebo or psychosocial treatment and had outcomes of at least 1 year and concluded, "early intervention with neuroleptics in first-break schizophrenic patients increases the likelihood of an improved long-term course."[11(p325)] Carpenter[4(p12)] disputes Wyatt's conclusion as being based largely on uncontrolled studies with "myriad confounds" that undermine "their relevance to understanding drug treatment effects on long-term course." In an exchange with Carpenter on the risks of medication-free research in schizophrenia, Wyatt[2] acknowledged that his hypothesis, that the presumed long-term benefit from initial antipsychotic treatment was due to a reduction in biological toxicity from unmedicated psychosis, was speculative.

The question of whether there is long-term harm from not immediately treating subjects with antipsychotic medications in early episode schizophrenia spectrum disorders has important research and clinical implications. In research, the implication is whether it is ethical to conduct medication-free studies. In clinical practice, the question is whether we should rush to treat early episodes (and even prodromal states) with antipsychotics, often before a clear diagnosis has become evident. Due to

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Table 1. Exclusion of Previously Reviewed Studies

Studies	Reasons for Exclusion		
	Multiepisode Sample	Lack of Concurrent Comparison Group	Drug-Withdrawal Study
Anzai et al. 1988[70]		X	
Aritome 1978[71]		X	
Astrup and Noreik 1966[72]		X	
Carpenter, McGlashan, and Strauss 1977[73]	X[a]		
Crow et al. 1986[75]			X
Curson et al. 1985[76]	X		X
Greenblatt et al. 1965[77]	X		
Huber et al. 1980[78]		X	
Johnson et al. 1983[79]	X		X
McWalter et al. 1961[80]		X	
Murakami 1971[81]		X	
Odegard 1964[82]		X	
Peterson and Olson 1964[83]		X	
Pritchard 1967a[84]		X	
Pritchard 1967b[85]		X	
Shimanzono and Toru 1968[86]		X	
Watt, Katz, and Shepherd 1983[87]	X	X	

[a]This study compared experimentally treated, multiepisode schizophrenia subjects to first-episode subjects in the World Health Organization (WHO) multisite International Pilot Study of Schizophrenia.[74]

the importance of this question and its implications, a quantitative reexamination of relevant good-quality evidence is undertaken.

Method

A comprehensive review of published literature was conducted to locate early episode treatment comparison studies in which at least 1 group was not initially medicated and with at least 1-year outcomes. Authors' original statistics and/or published data were used to calculate effect sizes (in the metric "*r*") for each outcome measure.[13–15*] An average effect size was calculated for each study. Study effect sizes were tested for heterogeneity and combined into a composite effect size estimate using Fisher's *F* transformation (to normalize the distribution of *r*) and inverse variance weights for small samples.[15(p49,eq3.24)] The overall mean was tested for significance, and a fixed effects confidence interval was constructed. Effect size magnitudes are small ($r = .10$), medium ($r = .30$), and large ($r = .50$).[16] A negative effect indicates better outcomes for the initially nonmedicated group.

Study Selection

Randomized studies provide the highest-quality evidence, yet with so few available, study selection criteria were relaxed to include quasi-experimental studies. This follows published guidelines for study inclusion in *Cochrane Systematic Reviews.*[17(sec5.2.3)] More nuanced guidelines are under development (see http://www.cochrane.dk/nrsmg/).

Studies were included if they (1) treated primarily first- and second-episode schizophrenia spectrum illnesses, (2) contained at least 1 medication-treated group and 1 comparison group with a no-medication trial during the same time period, and (3) reported at least 1-year follow-up results. Drug-withdrawal studies, in which all subjects were initially medicated, do not directly address the question of the long-term effects of medication postponement (since there was no medication-free group) and were therefore also excluded. These criteria led to the exclusion of 17 of the 22 studies reviewed by Wyatt[11] (Table 1).

In all, only 7 studies meeting the selection criteria were identified, consisting of 4 random assignment and 3 quasi-experimental studies. The 4 randomly assigned studies[18–21] and 1 of the quasi-experimental studies[22] were also reviewed by Wyatt. Two more recent quasi-experimental studies,[23,24] additional randomly assigned subjects in 1 study,[25] and 1 longer-term follow-up[26] were also included. The Swedish 1-year comparison of psychosocial to hospital treatment[27] was not included due to a trial without medication in both groups. Thus, neither studies with a medication-free trial in both groups, nor medication withdrawal studies, in which all subjects were initially medicated, contain the required contrast of a medicated to an initially nonmedicated group.

*For example, *r* is computed from a *t*-test statistic using the formula $r = (t^2 / t^2 + df)^{1/2}$, from an F-statistic as $r = (F/F + df\text{error})^{1/2}$, from a chi-square as $r = (\chi^2(1) / N)^{1/2}$, and from a standard normal as $r = Z / N^{1/2}$.

Table 2. Study Design and Treatment Comparison Components

Study	*N*	Design	Treatment Comparison	Maximum Time Off Medications	Length of Follow-Up
Wirt and Simon 1959[19]	39	Random	Placebo vs Medications in the Hospital	30 days	1 year
Schooler et al. 1967[21]	(254)	Random	Placebo vs Medications in the Hospital	6 weeks	1 year
May et al. 1976a, 1976b, 1981[20,30,31]; Wyatt, Green, and Tuma 1997[26]	22–225	Random	Psychotherapy, Hospital Milieu, vs Medications, Medications plus Psychotherapy	6–12 months	3–7 years
Rappaport et al. 1978[18]	80	Random	Hospital Milieu vs Medications in the Hospital	45 days	3 years
Bola and Mosher 2003[25]	106–129	Quasi-Experimental	Therapeutic Milieu vs Medications in the Hospital	6 weeks	2 years
Ciompi et al. 1992, 1993[23,34]	44	Quasi-Experimental	Therapeutic Milieu vs Medications in the Hospital	6 weeks	2 years
Lehtinen et al. 2000[24]	106	Quasi-Experimental	Family Intervention vs Family Intervention plus Medications	3 weeks	2 years

Review of Included Studies

The chronological review of included studies presented here is abbreviated. Due to the scarcity of available studies, an average effect size was calculated for each study, irrespective of the length of the various follow-up periods. Study effect estimates use Fisher's Z transformation of the effect size for each outcome variable weighted by the number of available cases. Study characteristics, including sample size, design, treatment comparison, maximum time off medications, and length of the follow-up period are presented in Table 2.

Minneapolis Veterans Administration Study

Wirt and Simon[19] randomly assigned 80 male first-admission DSM-I schizophrenia subjects to 4 treatments, including a hospital routine group receiving placebo in a hospital milieu for up to 30 days. One-year postdischarge outcomes for 79 of 80 patients found that, compared with the hospital routine group (n = 19), the chlorpromazine group (n = 20) had somewhat better social functioning (r = 0.18) and slightly lower work ratings (r = −0.03), indicating a small long-term advantage for the chlorpromazine-treated subjects (study effect: r = 0.08).

National Institute of Mental Health (NIMH) Collaborative Study

Cole and colleagues[28] conducted a large, multisite, double-blind, random assignment trial involving 344 mostly first admission (60%) schizophrenia patients assigned to receive neuroleptic medications or placebo in the hospital for 6 weeks. Higher attrition due to placebo treatment failures may have introduced a bias favoring placebo completers.

Comparing 1-year completers (n = 254), a smaller proportion of placebo-treated subjects had been rehospitalized.[21] However, neither rehospitalization rates nor a statistical test of this difference are reported, precluding the calculation of an effect size. As the largest and best controlled of available studies, for heuristic purposes, the negative direction of effect is included in Table 3 (study effect: r = "negative").

Camarillo State Hospital Study

May and colleagues[20,29–31] conducted an experimental comparison for 228 of 640 first-episode DSM-I schizophrenia subjects selected to be in the "middle third of the prognostic range"[29(p57)] and randomly assigned to 1 of 5 treatments, including milieu and psychotherapy treatment groups that did not receive antipsychotic medications.

At the 3-year follow-up, the combined antipsychotic-treated groups had better Menninger Health Sickness (r = 0.12) and work (r = 0.15) outcomes[20] than the combined milieu and psychotherapy groups. In a follow-up to this study, Wyatt and colleagues[26] reported 1-year (r = 0.09, n = 96) and 2-year postdischarge rehospitalization days (r = 0.15, n =96) and global assessment of functioning (GAF) at 6–7 years (r = 0.47, n = 22) for successive subsamples (study effect: r = 0.14).

Table 3. Effect Size by Study

Study	N[a]	Mean[b] Effect Size (r)
Wirt and Simon 1959[19]	39	0.08
Schooler et al. 1967[21]	(254)	(Negative)
May et al. 1976a, 1976b, 1981;[20,30,31] Wyatt, Green, and Tuma 1997[26]	22–225	0.14
Rappaport et al. 1978[18]	80	−0.18
Bola and Mosher 2003[25]	106–129	−0.19
Ciompi et al. 1992, 1993[23,34]	44	−0.09
Lehtinen et al. 2000[24]	106	−0.16
Median Effect Size	395–623	−0.13
Weighted Mean Effect Size[c,d]	395–623	−0.09[e] (.09)

Note: Range of study effect sizes: −.19 to .14.
[a]Number of subjects included in effect size estimates.
[b]A negative effect size indicated the initially nonmedicated group had better outcomes. Means calculated using Fisher's Z transformation.
[c]Effect sizes weighted by the inverse variance for each study.
[d]Chi-square test indicates nonheterogeneity of effect sizes ($\chi^2 = 2.32$, $df = 5$, not significant).
[e]$Z = -1.00$, not significant; fixed effects 95% CI: (−.27, .09).

Agnews State Hospital Study

Rappaport and colleagues[18] reported 3-year outcomes from a random assignment, double-blind comparison of chlorpromazine versus placebo in a special hospital milieu. Based on a clinical diagnosis of schizophrenia (presumably using DSM-II), 127 young, single males were admitted to the study (74% were first and second admissions). At the 3-year follow-up, fewer placebo (55%) than medication subjects (74%) were available, introducing an author-acknowledged potential for attrition bias.

Comparison of sample-size weighted mean (SD) clinical improvement scores for the combined placebo groups and the combined medication groups produces a nonsignificant t-test and a near zero effect size ($r = -0.03$). The 27% rehospitalization rate among placebo completers (11 of 41) is significantly lower than the 62% rate (34 of 39) among medication completers ($r = -.32$; study effect: $r = -0.18$).

Soteria Study

Mosher et al.[22,32] reported 2-year follow-up results of a quasi-experimental ("consecutive space-available") comparison of antipsychotic medications in the hospital to an intensive psychosocial milieu that minimized use of antipsychotics for an initial 6 weeks. Patients were young, unmarried, experiencing a first or second admission, and diagnosed with DSM-II schizophrenia. The Soteria study also collected data for a second randomly assigned cohort.[33] Soteria patients exhibited significantly better 2-year outcomes.[25] An effect size was calculated from the combined cohort reanalysis of 129 of 179 original subjects (study effect: $r = -0.19$).

Soteria Bern Study

Ciompi and colleagues[23,34] conducted a 2-year prospective pairwise matched case-control comparison of (N = 44) first-episode DSM-IIIR schizophrenia (65%) and schizophreniform subjects. Experimental subjects were treated in a special therapeutic milieu with minimal use of antipsychotics for 3–4 weeks. Approximately 60% of experimental subjects received antipsychotic medications in low doses (average 173 mg per day, chlorpromazine equivalent [CPZ] units).[34(p148)] Comparison subjects received usual hospital and medication treatment, with an average hospital subject's dose equaling 2615 CPZ mg per day.[34(p149)] At the 2-year follow-up there were no significant outcome differences (partly due to the small sample size). Outcome data[23(pp444–445,tables2&3)] for psychopathology ($r = 0.00$), independent (normal) living ($r = -0.23$), working full-time ($r = 0.11$), relapse ($r = -0.06$), and days of rehospitalization ($r = -0.23$) were used to calculated effect sizes (study effect: $r = -0.09$).

Finnish Need-Adapted Project

Lehtinen and colleagues[24] reported 2-year follow-up results from a quasi-experimental treatment comparison study for first-episode, DSM-IIIR nonaffective psychosis (41% schizophrenia). All sites treated patients with the Finnish need-specific treatment model, which included individual, family, and group therapy, while half of the sites also used a minimal neuroleptic protocol for an initial 3 weeks. An effort was made to not start neuroleptic treatment and, if started, dosages were usually low. Only 3% of experimental subjects received daily doses above 450 CPZ mg, compared to 13% of the usual medication group.[24] Sixty-four percent of subjects were available at the 2-year follow-up, with comparable rates of attrition.

The authors report statistically superior results[24(p317,table8)] for the experimental group on 2 of 5 outcome measures (proportion with less than 2 weeks of rehospitalization, $r = -0.25$; proportion with global assessment scale (GAS) score above 7, $r = -0.24$). Results for these and the 3 outcomes that were not statistically different (proportion of subjects with no psychotic symptoms, $r = -0.17$; proportion employed, $r = -0.02$; and proportion retaining GRIP on life, $r = -0.09$) were converted into effect size estimates. This study provides the only available long-term, quasi-experimental or better comparison of medication plus psychosocial treatment and psychosocial treatment only (study effect: $r = -0.16$).

Results

Individual study effects (see Table 3) range from $r = -0.19$ to $r = 0.14$ and are not significantly heterogeneous

($\chi^2 = 2.32$, $df = 5$, not significant [NS]). Combining effect sizes across studies (using inverse variance weights and Fisher's Z transformation[15]) produced a mean effect size of $r = -0.09$ (SE=.09) that was not significantly different from zero ($Z = -1.00$, NS, fixed effects 95% CI= −.27, .09).

Two plausible moderators of the composite effect size are quasi-experimental versus experimental study design and psychosocial versus placebo comparison treatment. Unfortunately, due the high correlation between these 2 variables (phi = −.77), it is not possible to disentangle their influences. Separate comparisons of quasi-experimental versus experimental studies (respectively, $r = -0.15$ versus $r = 0.01$; $t = 1.58$, $df = 4$, $p = .19$) and studies with active psychosocial versus placebo treatments (respectively, $r = -0.16$ versus $r = 0.11$, $t = -6.63$, $df = 4$, $p = .00$) were conducted. These comparisons indicate a small-medium effect size ($|r = 0.16|$) advantage for quasi-experimental over random assignment studies that is not statistically significant and a statistically significant medium effect-size advantage ($|r = 0.27|$) for active psychosocial treatment over placebo.

Limitations

Limitations restrict study conclusions in 6 areas: (1) a limited number of good-quality studies, (2) inclusion of only published studies, (3) diagnostic heterogeneity, (4) selection and/or attrition biases, (5) different treatment comparisons, and (6) treatment crossover.

The limited number of good-quality studies that address the long-term effects from initial medication treatment in early episode schizophrenia spectrum disorders is striking. Only 4 random assignment studies are available, with the largest and best-controlled study[21] ($N = 254$) reporting insufficient information to calculate an effect size. Incorporating only 6 studies with a total of 623 subjects does not provide a particularly sound basis for scientific conclusion. Equivocal results from these studies provide no definitive conclusion.

Publication bias has the potential to undermine composite effect estimates in the professional literature.[35] However, since the direction of publication bias tends to favor new treatments (in this case, antipsychotic treatment), it is unlikely that the effect of early antipsychotic treatment on long-term outcomes has been underestimated through the possible omission of unpublished studies.

Diagnostic criteria for schizophrenia range from DSM-I to DSM-IIIR: all studies included schizophrenia and schizophreniform subjects.

Selection bias occurs in at least 4 of the studies.[18–20,32] Differential attrition occurs in 4 of the 7 studies.[18,21,25,26] This raises concerns for both the internal validity and the generalizability of effect estimates.

Different treatment comparisons complicate effect size comparisons. Three of the studies[19,21,29] compared antipsychotic drug treatment in the hospital with hospital milieu treatment, 3 compared hospital drug treatment to an enhanced psychosocial milieu,[18,23,32] and 1 study compared psychosocial treatment plus medication with psychosocial treatment only.[24] Thus, while each study contains the central comparison of an initially medicated to an initially unmedicated group, differences in psychosocial treatment introduce additional variability into comparative estimates.

Finally, in most studies there was no control for post-discharge inpatient treatment, and the amount of treatment crossover is unknown. This means that, if readmitted prior to follow-up, an individual who was initially treated within a psychosocial (nonmedication) treatment protocol might subsequently be treated in a hospital with medications, or vice versa, with both situations attenuating the magnitude of long-term comparisons.

Discussion

The most striking observation in this review is the dearth of good-quality evidence that addresses the long-term effects of initial treatment with antipsychotic medication compared with short-term medication postponement in early episode schizophrenia research. The 6 available random and quasi-experimental studies, which contain a total of 623 subjects, contrast with much larger bodies of evidence in recent meta-analyses. For example, in a comparison of atypical versus conventional antipsychotic medications, Geddes and colleagues[36] included 52 randomized controlled trials and 12,649 subjects. Limited available evidence translates into limited confidence in the null finding of this study. This may be a type II error, failing to find a true long-term advantage from initial medication treatment due to limited data.

The finding of a small, negative, nonsignificant long-term effect for antipsychotic treatment in early episodes does not provide evidence of long-term harm from short-term research involving medication postponement. Nor does the inclusion of quasi-experimental studies change this conclusion, since aggregating only studies with random assignment yields a near-zero effect size ($r = 0.01$).

The medium-small effect size advantage observed in quasi-experimental studies ($|r = 0.16|$) suggests either (1) bias in the assignment of subjects to treatment in the quasi-experimental studies, (2) a benefit from psychosocial treatment, or (3) both. The repeated observation (by most investigators in both types of studies) of a subgroup of responders to psychosocial only or placebo treatment[18,20,21,24,34,37] suggests positive contributions to their overall group outcomes.[38]

None of the studies in this review were conducted with atypical antipsychotics, and, as far as is presently known,

there have been no long-term comparisons of atypical agents and placebo or psychosocial treatment in early episode schizophrenia. The few available long-term comparisons of conventional and atypical antipsychotics suggest comparable[39,40] or inconclusive results,[41] along with lower dropout[41,42] and improved cognition[43] among atypical medication–treated subjects. Schooler and colleagues[44] compared resperidone with haloperidol in first-episode psychosis and found a 13% lower relapse rate (42% vs 55%; effect size: $r = .06$) among risperidone-treated subjects over a median 206-day treatment period. This, combined with longer time to relapse and fewer extrapyramidal symptoms, suggests some advantages for the second generation antipsychotic (SGA) resperidone in treatment of first episodes. How this advantage extends to a comparison with initially nonmedicated first-episode subjects remains unclear. Results from the clinical antipsychotic trials of intervention effectiveness study[45] comparing SGAs to the first-generation medication perphenazine in chronic schizophrenia found comparable efficacy, along with high dropout rates, in both groups. In the aggregate these studies do not appear to establish a compelling advantage of SGAs over conventional antipsychotic medications that would imply harm to subjects from withholding SGAs for short, medication-free research trials in early acute episodes.

A reason for the presumed long-term advantage associated with early medication administration suggested by Wyatt is the plausible but speculative hypothesis that failing to medicate subjects may be "biologically toxic."[11(p347)] However, this hypothesis was generated from reanalysis of numerous studies without adequate control for threats to internal validity. The inclusion of poor-quality studies that bias results has long been of central concern in meta-analysis.[14,46] The field has gone to some lengths to investigate the biological toxicity hypothesis, yet Lieberman and Fenton's recent review concludes that "new information … militates against the hypothesis that measurable neurotoxicity and lifelong disability are frequent or inevitable consequences of untreated psychosis."[47(p1728)] In a related investigation, the question of whether a 4-week delay in administering antipsychotic medications resulted in poorer long-term outcomes was answered in the negative by Johnstone and colleagues.[48] That Browne and colleagues' comparison[49] of 2 groups of first-episode patients, those receiving medication for 30 days and the medication naive, found no differences on 2 measures of neurological dysfunction similarly corroborates this null finding.

Duration of untreated psychosis (DUP) is another area of research relevant to the considerations of (1) long-term harm from postponing medications, and (2) the hypothesis of psychosis-induced biological toxicity. While current knowledge suggests an association between DUP and time to symptom remission[50] and likelihood of achieving remission,[51] studies have been inconsistent in finding a relationship between DUP and outcome.[52] Warner[53] has suggested that the presumed relationship between DUP and outcome may be confounded by prognosis. The observed association between DUP and insidious onset[54] would seem to corroborate this point. In relation to cognitive deterioration, Amminger and colleagues[55] found an association with DUP, while others have not.[56–58] Hoff et al.[59] found no relationship between DUP and structural brain deficits in the first episode. Ho and colleagues[60] also failed to find evidence of biological toxicity in first-episode patients as a function of DUP. However, Friis and colleagues[61] have suggested that a disproportionate rate of refusal among long-DUP subjects may introduce a type II error into assessment of these relationships, failing to find an association where one exists. While these investigations proceed, no clear pattern of evidence indicating harm to subjects from short periods of medication-free research seems evident.

In multiepisode schizophrenia, as well, there is no clear evidence of long-term harm from short periods off medication. Gilbert et al.[62] reviewed 66 studies of neuroleptic withdrawal in multiepisode schizophrenia, reporting higher relapse rates and "mild and transient"[62(p173)] adverse effects of neuroleptic discontinuation, provided that medications were restarted quickly in response to symptom exacerbation. Similarly, in a 7-year follow-up study comparing placebo with medication continuation, Curson and colleagues[63] found higher rates of relapse among the placebo-treated subjects but no between-group differences on psychopathology measures.

On the benefit side, Carpenter and colleagues[9,64] have suggested numerous situations in which important scientific knowledge may be gained through medication-free research in schizophrenia regarding the medication noncompliant, those showing evidence of medication side effects, the elderly, single-episode patients, cases of spontaneous remission, the evaluation of the effects of psychosocial interventions, and so forth. The evaluation of new medications in comparison with placebo requires fewer subjects and reduces use of the inference that new medications are equally effective as established ones when they are not statistically different (affirming the null hypothesis). Wyatt[2] has also suggested areas of important research involving schizophrenia patients who are not taking antipsychotics: to identify first-episode patients who can safely be taken off medications where no further deterioration is expected, to reduce medication interactions, and in placebo trials involving new medications.

I have previously argued that the prospective identification of medication-free responders (spontaneous remitters, placebo responders, remitting nonaffective psychosis) may be both possible and advantageous in terms of improved outcomes and reduced medication exposure.[37,38]. Many investigators are interested in identifying which patients are candidates for medication withdrawal or low-dose treatment in both first- and

multiple-episode schizophrenia.[64–67]. The heterogeneity of treatment response in schizophrenia itself argues for a more nuanced approach to developing treatment subgroup knowledge that promotes theory development, diagnostic refinement, and a reduction in heterogeneity.

In terms of safety, Carpenter and colleagues[4,68,69] have suggested protocols for conducting medication-free research that minimize risks to human subjects, which include appropriate patient selection, careful informed consent procedures, use of the shortest possible drug-free period, and prior specification of criteria for instituting drug treatment if inadequate response or clinical deterioration ensues.[4,69]

In the absence of substantive evidence of long-term harm from short periods of medication-free research in schizophrenia, a categorical prohibition of medication-free research in early episode schizophrenia on the ethical grounds of harm to human subjects should probably be reconsidered. A "middle ground" proposed by Emanuel and Miller[7] involves assessing the risks and benefits of individual medication-free research protocols, which would require compelling reasons, no serious harm to subjects, and provisions to manage risk.

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