SHORT COMMUNICATION

Chronic low-grade peripheral inflammation is associated with ultra resistant schizophrenia. Results from the FACE-SZ cohort

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Abstract

A high rate of patients with schizophrenia (SZ) does not sufficiently respond to antipsychotic medication, which is associated with relapses and poor outcomes. Chronic peripheral inflammation has been repeatedly associated with schizophrenia risk and particularly to poor responders to treatment as usual with cognitive impairment in SZ subjects. The objective of present study was to confirm if ultra resistance to treatment in schizophrenia (UTRS) was associated to chronic peripheral inflammation in a non-selected sample of community-dwelling outpatients with schizophrenia. Participants were consecutively included in the network of the FondaMental Expert Centers for Schizophrenia and received a thorough clinical assessment, including recording of current treatment. Current psychotic symptomatology was evaluated by the Positive and Negative Syndrome scale for Schizophrenia (PANSS). UTRS was defined by current clozapine treatment + PANSS total score ≥ 70. Functioning was evaluated by the Global Assessment of Functioning scale. High sensitivity CRP (hs-CRP) was measured for each participant as a proxy to define peripheral low-grade inflammation. 609 stabilized community-dwelling SZ subjects (mean age = 32.5 years, 73.6% male gender) have been included. 60 (9.9%) patients were classified in the UTRS group. In multivariate analyses, UTRS has been associated independently with chronic peripheral inflammation (OR = 2.6 [1.2–5.7], $p = 0.01$), illness duration (OR = 1.1 [1.0–1.2], $p = 0.02$) and impaired functioning (OR = 0.9 [0.9–0.9], $p = 0.0002$) after adjustment for age, sex, current daily tobacco smoking, metabolic syndrome and antidepressant consumption. Peripheral low-grade inflammation is associated with UTRS. Future studies should explore if anti-inflammatory strategies are effective in UTRS with chronic low-grade peripheral inflammation.

Keywords Resistant schizophrenia · Inflammation · Functioning

Introduction

For most affected individuals, schizophrenia (SZ) is a chronic and disabling disorder. One of the most important predictors of relapse in schizophrenia is the response to antipsychotic medication, known to be highly variable in schizophrenia. The definition of treatment resistance

remains controversial in spite of its importance [16], for review see [36]). One in three patients is classified as treatment-resistant schizophrenia [27, 30]. Clozapine is still considered to date as the most effective antipsychotic [47] and a meta-analysis confirmed the largest effect size among the newer generation antipsychotics [25]. Since the pivotal study by Kane et al. [19] found that about a third of stringently defined treatment-resistant patients responded to clozapine, it has been the gold standard medication in this specific population and is now recommended in international therapeutic guidelines [1, 14, 13, 16, 22, 26, 28, 38, 40, 44]. However, 40% still remain classified as resistant to clozapine, which has been called "ultra resistance to treatment in

schizophrenia" (UTRS) [42]. The pathophysiological bases of UTRS remain largely to be elucidated [48].

Among the factors associated with resistance to antipsychotics, chronic low-grade peripheral inflammation has received increased interest during the last decade [12, 23]. Inflammatory blood markers have been recently shown to predict poor treatment response to antipsychotics [10, 32, 33], for review see [12]). In clinical practice, peripheral low-grade inflammation is measured by an elevated blood level of highly sensitive C-reactive protein (hs-CRP) [29]. CRP is a common final denominator in the inflammation cascade [29] and has been associated with increased SZ risk in recent meta-analyses [9, 18]. High blood CRP level has also been associated with cognitive impairment, a major source of disability in schizophrenia [6], and a large set of data has confirmed that anti-inflammatory add-on strategies are effective in improving SZ symptomatology [11, 34, 43]. If UTRS is associated with peripheral low-grade inflammation, it may be reasonably hypothesized that anti-inflammatory strategies should be useful to improve the outcomes of this specific population.

The objectives of the present study were to determine the prevalence of UTRS in a large non-selected sample of stabilized community-dwelling SZ outpatients, and to determine whether UTRS was associated with peripheral low-grade inflammation.

Population and methods

Study design

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles), set up by a scientific cooperation foundation in France, the FondaMental Foundation (http://www.fondation-fondamental.org) and pioneered by the French Ministry of Research in order to create a platform that links thorough and systematic assessment to research [41].

Study population

Consecutive clinically stable patients (defined by no hospitalization and no treatment changes during the 4 weeks before evaluation) with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder were consecutively included in the study. Diagnosis was confirmed by two trained psychiatrists of the Schizophrenia Expert Centres network. All subjects were referred by their general practitioner or psychiatrist who subsequently received a

detailed evaluation report with suggestions for personalized interventions.

Patients with a history of neurological disorders (including stroke, epilepsy and head injury) or all non-psychiatric concurrent illnesses affecting the central nervous system and on-going and treated inflammatory disorder such as lupus, rheumatoid arthritis or acute infectious disorder were not included in the present study.

Data collected

Patients were interviewed by members of the specialized multidisciplinary team of the Expert Center. Diagnoses interviews were carried out by two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0). Information about education, onset and course of the illness, body mass index and comorbidities were recorded.

Schizophrenic symptomatology was assessed using the Positive And Negative Syndrome Scale (PANSS) [21]. Current depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDRS) [2]. This scale was specifically designed to identify specific depressive symptomatology that cannot be related to negative symptoms of schizophrenia. Manic symptoms were evaluated using the Young Mania Rating Scale (YMRS) [49]. Daily global functioning was evaluated with the Global Assessment of Functioning Scale (GAF) [45]. Ongoing psychotropic treatment was recorded. Alcohol and/or cannabis disorders were defined according to the SCID 1.0. Self-reported adherence to pharmacological treatment was evaluated using the French translation of the MARS [31].

UTRS definition

UTRS was defined by current clozapine treatment and a mean PANSS score ≥ 70, which is suggested to correspond to "moderately to severely ill" patients [24].

Measurements

A blood draw for routine blood exam was performed and triglycerides, LDL, HDL and total cholesterol as well as glucose (if patients confirmed fasting for at least 10 h) were collected. High sensitivity CRP (hs-CRP) was measured with an assay using nephelometry (Dade Behring) blinded to schizophrenia status. Abnormal CRP level was defined as > 3 mg/L [8].

Metabolic syndrome (MetS) definition

Sitting blood pressure (BP) and anthropometrical measurements were recorded in the Expert Centers. Two BP

measurements were made 30 s apart in the right arm after the participant had sat and rested for at least 5 min. A third BP measurement was made only when the first two BP readings differed by more than 10 mm Hg. The average of the two closest readings was used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing. This was performed with a tape equipped with a spring-loaded mechanism to standardize tape tension during measurement. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Overnight fasting blood was collected for metabolic profiles analysis. Fasting levels of serum triglyceride (TG) and fasting plasma glucose were measured by an automated system, and serum high-density lipoprotein cholesterol (HDL-C) level was measured by electrophoresis. The diagnosis of metabolic syndrome was defined according to the modified criteria of the International Diabetes Federation (IDF) [3], which requires the presence of three or more of the following five criteria: high waist circumference (> 94 cm for men and > 80 cm for women), hypertriglyceridemia (≥ 1.7 mM or on lipid lowering medication), low HDL cholesterol level (< 1.03 mM in men and < 1.29 mM in women), high blood pressure (≥ 130/85 mmHg or on antihypertensive medication), high fasting glucose concentration (≥ 5.6 mM or on glucose-lowering medication).

Ethical concerns

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18, 2010). All data were collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

Statistical analysis

Socio-demographics and clinical characteristics and treatments are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data were examined for normal distribution with the Shapiro–Wilk test and for homogeneity of variance with the Levene test. Comparisons between ultra resistant and non-ultra resistant individuals regarding demographic, clinical characteristics were performed using the Chi square test for categorical variables. Continuous variables were analysed with Student *t* tests for normally distributed data and in case of normality violation, additional Mann–Whitney tests were performed to confirm the result.

Variables with *p* values < 0.20 in univariate analysis were included in the multivariate logistic regression model of factors associated with ultra resistant schizophrenia. Sex and age were forced into the final model as confounding factors. This study was a confirmatory analysis. No correction for multiple testing has therefore been carried out, which is consistent with recommendations [4]. Analyses were conducted using SAS (release 9.3; SAS Statistical Institute, Cary, NC). All statistical tests were two-tailed, with α level set at 0.05.

Results

609 stabilized community-dwelling SZ subjects (mean age = 32.5 years, 73.6% male gender) have been included. Overall, 60(9.9%) patients were classified in the UTRS group (Table 1). UTRS has been significantly associated with positive, negative and cognitive scores (all *p* < 0.0001), with excitement score (*p* = 0.003) but not with depressive score (*p* = 0.08). Compared to non-UTRS, patients of the UTRS group were found to have higher illness duration (13.0 vs. 10.6 years, *p* = 0.01), more frequently paranoid delusion (56.9 vs 53.1%, *p* = 0.002), grandiosity delusion (23.4 vs. 10.6%, *p* = 0.009), mystic delusion (23.1 vs.11.7%, *p* = 0.02), auditory hallucinations (*p* = 0.02) and disorganized behavior (43.9 vs. 25.2%, *p* = 0.005). No difference on catatonia, somatic delusion, guilty delusion, erotomania, jealousy delusion, reference delusion, visual and cenesthetic hallucinations, avolia, alogia and blunted affect has been found (all p > 0.05). In the present study, no significant difference of hs-CRP levels has been found between the subgroup of clozapine-treated non-UTRS group and UTRS group (all being administered clozapine by definition) (44.4 vs. 46.3%, *p* = 0.88).

In multivariate analyses, UTRS has been associated independently with chronic peripheral inflammation (OR = 2.6 [1.2–5.7], *p* = 0.01), impaired functioning (OR = 0.9 [0.91–0.97], *p* = 0.0002) and illness duration (OR = 1.1 [1.0–1.2], *p* = 0.02) after adjustment for age, sex, current daily tobacco smoking, metabolic syndrome and antidepressant consumption. The mean CRP levels in UTRS and non-UTRS groups were presented in Fig. 1. 45 patients (8.2%) received clozapine treatment without being ultra treatment resistant. No difference of clozapine blood levels has been found between UTRS and no UTRS groups (mean 523.7 mg/mL (SD = 320) in clozapine non-remitters vs. 460.0 (SD = 380.7) in clozapine remitters, *p* = 0.56). Antipsychotic consumption was not included in the multivariate model because it was not significantly associated with UTRS in univariate analysis. However, forcing antipsychotic consumption in the model did not change the results (hsCRP OR = 2.1 [1.0–4.2], *p* = 0.04).

Table 1 Factors associated with Ultra Treatment Resistance in Schizophrenia (UTRS) in a cohort of 609 community-dwelling stabilized outpatients with schizophrenia (SZ)

	Whole sample	No UTRS (n=549, 90.1%)	UTRS (n=60, 9.9%)	p*	Multivariate analysis	
					OR (95% CI)	p*
Demographic characteristics						
Gender						
Male	444 (73.6%)	403 (73.4%)	46 (76.7%)	0.59	1 (ref)	0.90
Female	159 (26.4%)	146 (26.6%)	14 (23.3%)		1.1 (0.5–2.4)	
Age, mean (SD)	32.5 (9.8)	32.3 (9.5)	33.7 (9.1)	0.29	1.0 (0.9–1.1)	0.20
Disease characteristics						
History of SZ or BP in parenthood, n(%)	46 (7.6%)	41 (7.5%)	5 (8.3%)	0.81		
Age of SZ onset (years), mean (SD)	21.6 (6.4)	21.7 (6.5)	20.7 (5.4)	0.23		
Illness duration, mean (SD)	10.8 (8.1)	**10.6 (8.2)**	**13.0 (7.6)**	**0.03**	**1.1 (1.0–1.2)**	**0.02**
Duration of untreated psychosis, mean (SD)	1.4 (3.2)	1.5 (3.4)	0.9 (1.8)	0.31		
Depressive symptoms (CDRS score), mean (SD)	4.0 (4.3)	4.0 (4.3)	4.3 (4.7)	0.62		
Manic symptoms (YMRS score), mean (SD)	2.3 (3.9)	2.3 (4.0)	2.7 (4.1)	0.45		
Global functioning (GAF), mean (SD)	48.7 (13.0)	**49.6 (13.0)**	**40.4 (9.7)**	**<0.0001**	**0.9 (0.91–0.97)**	**0.0002**
Comorbidities						
Current daily tobacco smoking, n(%)						
No	262 (44.9%)	**229 (43.6%)**	**33 (55.9%)**	**0.07**	0.5 (0.2–1.0)	0.06
Yes	321 (55.1%)	**296 (56.4%)**	**26 (44.1%)**			
Current alcohol use disorder*, n(%)	37 (8.7%)	32 (8.3%)	5 (12.2%)	0.40		
Current cannabis use disorder*, n(%)	37 (9.5%)	36 (10.0%)	1 (3.3%)	0.34		
Metabolic syndrome, n(%)	121 (23.3%)	102 (21.7%)	19 (40.4%)	0.004	1.8 (0.8–4.0)	0.15
Abnormal CRP**, n(%)	103 (26.2%)	**86 (24.3%)**	**17(43.6%)**	**0.009**	**2.6 (1.2–5.7)**	**0.01**
Treatments at baseline						
Adherence to medication (MARS score), mean (SD)	6.3 (2.2)	6.3 (2.2)	6.5 (1.8)	0.63		
First generation antipsychotic, n(%)	158 (26.2%)	148 (27.0%)	12 (20.0%)	0.25		
Antidepressant, n(%)	189 (31.3%)	167 (30.4%)	25 (41.7%)	0.08	1.9 (0.9–4.1)	0.09
Mood stabilizer, n(%)	109 (18.1%)	100 (18.2%)	11 (18.3%)	0.98		

UTRS was defined by current clozapine treatment + mean PANSS score ≥ 70

Significant associations ($p < 0.05$) are in bold

PANSS Positive and Negative Syndrome Scale for Schizophrenia, *MARS* Medication Adherence Rating Scale score, *YMRS* Young Mania Rating Scale, *CDRS* Calgary Depression Rating Scale Score, *GAF* Global Assessment of Functioning score, *SZ* schizophrenia, *BP* bipolar disorder

*Structured Clinical Interview for Mental Disorders (SCID 1.0)

**hs-CRP blood levels ≥ 3 mg/L

Discussion

Our major findings may be summarized as follows: in a large non-selected community-dwelling sample of 609 SZ subjects, UTRS has been identified in almost 10% of the subjects and was independently associated with chronic peripheral inflammation and impaired functioning.

Almost 10% of our sample has been identified as UTRS. This is consistent with previous data mentioned in the rationale, which have suggested that one-third of the patient were treatment resistant and 40% of them (= 12%) were ultra-resistant [42].

UTRS has been associated with impaired functioning in the present study. This result confirms the clinical significance of our definition of resistance into treatment. UTRS has been extensively suggested as a separate schizophrenia subtype and has been associated with a specifically impaired functioning [17], for review see [46]).

UTRS has been shown to be associated with peripheral inflammation for the first time in the present study. Some previous studies have yielded indirect clues suggesting that abnormal inflammatory markers may predict treatment non-response in schizophrenia [32, 33]. Moreover, electroconvulsive therapy, a treatment that has shown effectiveness in resistant schizophrenia, has recently shown to modify
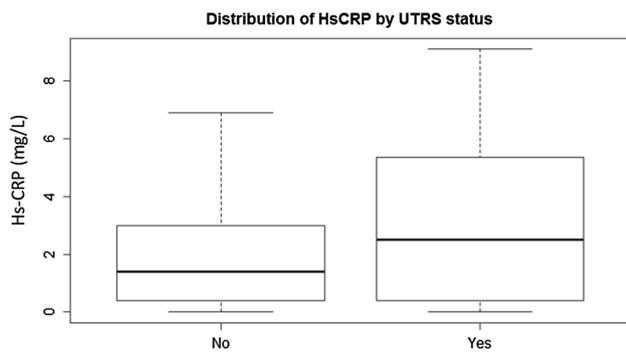
Fig. 1 Mean highly senstive C-Reactive Protein levels (hs-CRP) differences between ultra-treatment resistant schizophrenia (UTRS) and non-UTRS stabilized outpatients with schizophrenia

peripheral inflammatory markers [20]. However, a previous study found no association between peripheral inflammation and resistant SZ as defined by clozapine initiation or hospital admission due to schizophrenia after having received at least 2 prior antipsychotic monotherapy trials of adequate duration) [15]. This discrepancy in the results is probably due to the discrepancy between definitions, the present study focusing on ultra-resistant SZ and not resistant SZ only.

Ultra-resistance has been associated with illness duration, which is consistent with the results of previous studies supporting the staging model [35].

Altogether, the present results combined with literature data suggest that anti-inflammatory strategies may be useful in UTRS. Celecoxib has been the most studied anti-inflammatory add-on agent in SZ [43]. Some trials are ongoing to determine if aspirin, N-acetyl-cysteine, minocycline and omega 3 fatty acids may be useful anti-inflammatory add-on strategies for this specific population [7, 11, 39].

Limits

These results should be taken with caution. As our study has a cross-sectional design, no causal link can be definitely inferred. Exercise, diet and gut permeability have been suggested as risk factors for peripheral inflammation [5] and have not been explored in the present study, as well as hormonal contraception, omega 3 fatty acid or vitamin D consumption (that may alleviate inflammation). As the dosage of the other markers of inflammation is not recommended in daily practice in France, other inflammatory markers (including interleukin IL-6 and Tumor Necrosis Factor TNFα) were not measured in our study. Our sample may not be representative of all patients with schizophrenia, particularly because institutionalized; hospitalized or very handicapped patients (making thorough assessment difficult) were not referred to the expert centers. HsCRP was the only inflammatory marker in the present study. Given that

clozapine has been described to have immunomodulatory effects [37], these results should be confirmed with other markers like IL-6 and TNF-alpha. However, no association between clozapine and increased CRP has been found in the present study.

Strengths

The use of homogenous and exhaustive standardized diagnostic protocols across the centers and inclusion of a large number of potential confounding factors in the multivariate analysis (socio-demographic variables, psychotic and mood symptomatology, adherence to treatment, addictive behaviors) may be mentioned in the strengths of the present work. In the end, our national multi-centric sample of SZ patients referred to the Expert Centers may be underscored as another strength.

Conclusion

UTRS is independently associated with peripheral low-grade inflammation in stabilized SZ community-dwelling subjects. Future studies should explore if anti-inflammatory add-on strategies are effective in UTRS.

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Compliance with ethical standards

Conflict of interest   None.

References

1. Abidi S, Mian I, Garcia-Ortega I, Lecomte T, Raedler T, Jackson K, Pringsheim T, Addington D (2017) CPA guidelines for the pharmacological treatment of schizophrenia spectrum and other psychotic disorders in children and youth. Can J Psychiatry 62(9):635–647. https://doi.org/10.1177/0706743717720197

2. Addington D, Addington J, Maticka-Tyndale E (1993) Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry (Suppl 22):39–44

3. Alberti KGMM., Zimmet P, Shaw J (2006) Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 23:469–480. https://doi.org/10.1111/j.1464-5491.2006.01858.x

4. Bender R, Lange S (2001) Adjusting for multiple testing—when and how? J Clin Epidemiol 54:343–349. https://doi.org/10.1016/S0895-4356(00)00314-0

5. Berk M, Williams J, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M (2013) So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 11:200. https://doi.org/10.1186/1741-7015-11-200

6. Bulzacka E, Boyer L, Schürhoff F, Godin O, Berna F, Brunel L, Andrianarisoa M, Aouizerate B, Capdevielle D, Chéreau-Boudet I, Chesnoy-Servanin G, Danion J-M, Dubertret C, Dubreucq J, Faget C, Gabayet F, Le Gloahec T, Llorca P-M, Mallet J, Misdrahi D, Rey R, Richieri R, Passerieux C, Roux P, Yazbek H, Leboyer M, Fond G, FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) Group (2016) Chronic peripheral inflammation is associated with cognitive impairment in schizophrenia: results from the multicentric FACE-SZ dataset. Schizophr Bull. https://doi.org/10.1093/schbul/sbw029

7. Cuéllar-Barboza AB, Sánchez-Ruiz JA, Corral PM (2017) Use of Omega-3 polyunsaturated fatty acids as augmentation therapy in treatment-resistant schizophrenia. Prim Care Companion CNS Disord. https://doi.org/10.4088/PCC.16l02040

8. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SRK, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CDA, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet Lond Engl 375:2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9

9. Fernandes BS, Steiner J, Bernstein H-G, Dodd S, Pasco JA, Dean OM, Nardin P, Gonçalves C-A, Berk M (2016) C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry 21:554–564. https://doi.org/10.1038/mp.2015.87

10. Fernandez-Egea E, Vértes PE, Flint SM, Turner L, Mustafa S, Hatton A, Smith KGC, Lyons PA, Bullmore ET (2016) Peripheral immune cell populations associated with cognitive deficits and negative symptoms of treatment-resistant schizophrenia. PLoS ONE 11:e0155631. https://doi.org/10.1371/journal.pone.0155631

11. Fond G, Hamdani N, Kapczinski F, Boukouaci W, Drancourt N, Dargel A, Oliveira J, Le Guen E, Marlinge E, Tamouza R, Leboyer M (2014) Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. Acta Psychiatr Scand 129:163–179. https://doi.org/10.1111/acps.12211

12. Fond G, d'Albis M-A, Jamain S, Tamouza R, Arango C, Fleischhacker WW, Glenthøj B, Leweke M, Lewis S, McGuire P, Meyer-Lindenberg A, Sommer IE, Winter-van Rossum I, Kapur S, Kahn RS, Rujescu D, Leboyer M (2015) The promise of biological markers for treatment response in first-episode psychosis: a systematic review. Schizophr Bull 41:559–573. https://doi.org/10.1093/schbul/sbv002

13. Hasan A, Wobrock T, Gaebel W, Janssen B, Zielasek J, Falkai P, Germany Society of Psychotherapy and Psychosomatics (DGPPN), German Association of Psychiatry (2013) National and international schizophrenia guidelines. Update 2013 regarding recommendations about antipsychotic pharmacotherapy. Nervenarzt 84:1359–1360, 1362–1364, 1366–1368. https://doi.org/10.1007/s00115-013-3913-6

14. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Thibaut F, Möller H-J, WFSBP Task Force on Treatment Guidelines for Schizophrenia (2015) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of schizophrenia. Part 3: Update 2015 Management of special circumstances: depression, suicidality, substance use disorders and pregnancy and lactation. World J Biol Psychiatry 16:142–170. https://doi.org/10.3109/15622975.2015.1009163

15. Horsdal HT, Wimberley T, Benros ME, Gasse C (2017) C-reactive protein levels and treatment resistance in schizophrenia—a Danish Population-based Cohort Study. Hum Psychopharmacol. https://doi.org/10.1002/hup.2632

16. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJM, Birnbaum ML, Bloomfield MAP, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F, Glenthøj BY, Graff-Guerrero A, Hallak JEC, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J, Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Möller H-J, Nakajima S, Pantelis C, Reis Marques T, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas N, Üçok A, Umbricht D, Walters JTR, Kane J, Correll CU (2017) Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry 174:216–229. https://doi.org/10.1176/appi.ajp.2016.16050503

17. Iasevoli F, Giordano S, Balletta R, Latte G, Formato MV, Prinzivalli E, De Berardis D, Tomasetti C, de Bartolomeis A (2016) Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones. Prog Neuropsychopharmacol Biol Psychiatry 65:34–48. https://doi.org/10.1016/j.pnpbp.2015.08.010

18. Inoshita M, Numata S, Tajima A, Kinoshita M, Umehara H, Nakataki M, Ikeda M, Maruyama S, Yamamori H, Kanazawa T, Shimodera S, Hashimoto R, Imoto I, Yoneda H, Iwata N, Ohmori T (2016) A significant causal association between C-reactive protein levels and schizophrenia. Sci Rep 6:26105. https://doi.org/10.1038/srep26105

19. Kane J, Honigfeld G, Singer J, Meltzer H (1988) Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796

20. Kartalci S, Karabulut AB, Erbay LG, Acar C (2016) Effects of electroconvulsive therapy on some inflammatory factors in patients with treatment-resistant schizophrenia. J ECT 32:174–179. https://doi.org/10.1097/YCT.0000000000000303

21. Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276

22. Keating D, McWilliams S, Schneider I, Hynes C, Cousins G, Strawbridge J, Clarke M (2017) Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. BMJ Open 7:e013881. https://doi.org/10.1136/bmjopen-2016-013881

23. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015) Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2:258–270. https://doi.org/10.1016/S2215-0366(14)00122-9

24. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR (2005) What does the PANSS mean? Schizophr Res 79:231–238. https://doi.org/10.1016/j.schres.2005.04.008

25. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet Lond Engl 382:951–962. https://doi.org/10.1016/S0140-6736(13)60733-3

26. Leucht S, Winter-van Rossum I, Heres S, Arango C, Fleischhacker WW, Glenthøj B, Leboyer M, Leweke FM, Lewis S, McGuire P, Meyer-Lindenberg A, Rujescu D, Kapur S, Kahn RS, Sommer IE (2015) The optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) trial: rationale for its methodology and a review of the effectiveness of switching antipsychotics. Schizophr Bull 41:549–558. https://doi.org/10.1093/schbul/sbv019

27. Lindenmayer J-P, Liu-Seifert H, Kulkarni PM, Kinon BJ, Stauffer V, Edwards SE, Chen L, Adams DH, Ascher-Svanum H, Buckley PF, Citrome L, Volavka J (2009) Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. J Clin Psychiatry 70:990–996. https://doi.org/10.4088/JCP.08m04221

28. Lo TL, Warden M, He Y, Si T, Kalyanasundaram S, Thirunavukarasu M, Amir N, Hatim A, Bautista T, Lee C, Emsley R, Olivares J, Yang YK, Kongsakon R, Castle D (2016) Recommendations for the optimal care of patients with recent-onset psychosis in the Asia-Pacific region. Asia-Pac Psychiatry 8:154–171. https://doi.org/10.1111/appy.12234

29. Lopresti AL, Maker GL, Hood SD, Drummond PD (2014) A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. Prog Neuropsychopharmacol Biol Psychiatry 48:102–111. https://doi.org/10.1016/j.pnpbp.2013.09.017

30. Meltzer HY (1997) Treatment-resistant schizophrenia—the role of clozapine. Curr Med Res Opin 14:1–20. https://doi.org/10.1185/03007999709113338

31. Misdrahi D, Verdoux H, Llorca P-M, Baylé F-J (2004) Therapeutic adherence and schizophrenia: the interest of the validation of the French translation of Medication Adherence Rating Scale (MARS). Encephale 30:409–410

32. Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A, Marques TR, Zunszain PA, Morgan C, Murray RM, Pariante CM, Dazzan P (2015) Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. Schizophr Bull 41:1162–1170. https://doi.org/10.1093/schbul/sbv028

33. Nishimon S, Ohnuma T, Takebayashi Y, Katsuta N, Takeda M, Nakamura T, Sannohe T, Higashiyama R, Kimoto A, Shibata N, Gohda T, Suzuki Y, Yamagishi S-I, Tomino Y, Arai H (2017) High serum soluble tumor necrosis factor receptor 1 predicts poor treatment response in acute-stage schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 76:145–154. https://doi.org/10.1016/j.pnpbp.2017.03.006

34. Nitta M, Kishimoto T, Müller N, Weiser M, Davidson M, Kane JM, Correll CU (2013) Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. Schizophr Bull 39:1230–1241. https://doi.org/10.1093/schbul/sbt070

35. Ortiz BB, Eden FDM, de Souza ASR, Teciano CA, de Lima DM, Noto C, Higuchi CH, Cogo-Moreira H, Bressan RA, Gadelha A (2017) New evidence in support of staging approaches in schizophrenia: differences in clinical profiles between first episode, early stage, and late stage. Compr Psychiatry 73:93–96. https://doi.org/10.1016/j.comppsych.2016.11.006

36. Peuskens J (1999) The evolving definition of treatment resistance. J Clin Psychiatry 60(Suppl 12):4–8

37. Pollmächer T, Hinze-Selch D, Mullington J (1996) Effects of clozapine on plasma cytokine and soluble cytokine receptor levels. J Clin Psychopharmacol 16:403–409

38. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M (2017) Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry. https://doi.org/10.1177/0706743717720448

39. Rossell SL, Francis PS, Galletly C, Harris A, Siskind D, Berk M, Bozaoglu K, Dark F, Dean O, Liu D, Meyer D, Neill E, Phillipou A, Sarris J, Castle DJ (2016) N-acetylcysteine (NAC) in schizophrenia resistant to clozapine: a double blind randomised placebo controlled trial targeting negative symptoms. BMC Psychiatry 16:320. https://doi.org/10.1186/s12888-016-1030-3

40. Samalin L, Abbar M, Courtet P, Guillaume S, Lancrenon S, Llorca P-M (2013) French Society for Biological Psychiatry and Neuropsychopharmacology task force: formal consensus for the prescription of depot antipsychotics. Encephale 39(Suppl 4):189–203. https://doi.org/10.1016/S0013-7006(13)70121-0

41. Schürhoff F, Fond G, Berna F, Bulzacka E, Vilain J, Capdevielle D, Misdrahi D, Leboyer M, Llorca P-M, FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) Collaborators (2015) A National network of schizophrenia expert centres: an innovative tool to bridge the research–practice gap. Eur Psychiatry. https://doi.org/10.1016/j.eurpsy.2015.05.004

42. Siskind D, Siskind V, Kisely S (2017) Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can J Psychiatry. https://doi.org/10.1177/0706743717718167

43. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS (2013) Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull 40(1):181–191

44. Stahl SM, Morrissette DA, Citrome L, Saklad SR, Cummings MA, Meyer JM, O'Day JA, Dardashti LJ, Warburton KD (2013) "Meta-guidelines" for the management of patients with schizophrenia. CNS Spectr 18:150–162. https://doi.org/10.1017/S109285291300014X

45. Startup M, Jackson MC, Bendix S (2002) The concurrent validity of the Global Assessment of Functioning (GAF). Br J Clin Psychol 41:417–422

46. Strassnig MT, Harvey PD (2014) Treatment resistance and other complicating factors in the management of schizophrenia. CNS Spectr 19(Suppl 1):16–23; quiz 13–15, 24. https://doi.org/10.1017/S1092852914000571

47. Sultan RS, Olfson M, Correll CU, Duncan EJ (2017) Evaluating the effect of the changes in FDA guidelines for clozapine monitoring. J Clin Psychiatry. https://doi.org/10.4088/JCP.16m11152

48. Suzuki T, Uchida H, Watanabe K, Kashima H (2011) Factors associated with response to clozapine in schizophrenia: a review. Psychopharmacol Bull 44:32–60

49. Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429–435. https://doi.org/10.1192/bjp.133.5.429

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