Euro Global Summit and Medicare Expo on
Psychiatry
July 20-22, 2015 Barcelona, Spain

# Pharmacological Managment of Treatment Resistant Schizophrenia

Jean-Marie Batail - France

21st July 2015

Comportement et Noyaux Gris Centraux

Centre Hospitalier Guillaume RÉGNIER

UNIVERSITÉ DE RENNES 1

# Introduction

A **chronic** and **debilitating** illness …

- Lifetime prevalence of around **0,7%**.
- Beginning : **16 - 30 years**.
- High mortality rates with a loss of 12 to 15 years of life expectancy

*Mc Grath et al., Epidemiol Rev, 2008;*
*van Os et Kapur, The Lancet, 2009;*

…potentially **treatment resistant**

- Partial response to pharmacological interventions (30 à 60%).
- Longer hospitalisations, direct and indirect cost, worsened quality of life.

World Health Organization

- 3rd cause of years lived with disability.
- Major handicap in social, family and professionnal life.

# What definition of response / resistance in schizophrenia ?

**High heterogeneity**:

- Scales (PANSS, BPRS, CGI).
- Score thresholds (-20% to -50% scores baseline PANSS et BPRS).
- Duration of treatment (4 to 12 weeks).

Response rates in TRS : **0% - 76%** (Suzuki et al., 2011).

Few studies based on **global functionning**

-> GAF (Ciapparelli, 2003).

## Definitions of treatment-resistant schizophrenia

**Kane et al. (1988)[8]**

- Persistent positive symptoms
- Current presence of at least moderately severe illness (BPRS >45, CGI >4)
- Persistence of illness: no stable period of good social/ occupational functioning in past 5 years
- Drug-refractory condition: three periods of treatment in preceding 5 years with first-generation antipsychotics in doses greater than 1000 mg chlorpromazine equivalents/day, for 6 weeks without significant improvement

**Conley and Kelly (2001)[9]**

- Drug-refractory condition: at least two previous antipsychotic drug trials of 4–6 weeks' duration at 400–600 mg/day (chlorpromazine equivalents, mg/day) with no clinical improvement
- Persistence of illness: more than 5 years with no period of social or occupational functioning
- Persistent psychotic symptoms (BPRS 18 >45, CGI >4)

**National Institute of Clinical Excellence (2002)[10]**

- Lack of a satisfactory clinical improvement despite the sequential use of the recommended doses for 6–8 weeks of at least two antipsychotic drugs, at least one of which should be a second-generation antipsychotic

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression scale.

*Barnes et Dursun, 2008*

# What strategy ?

Clinical review

## Pharmacotherapy of treatment-resistant schizophrenia: a clinical perspective

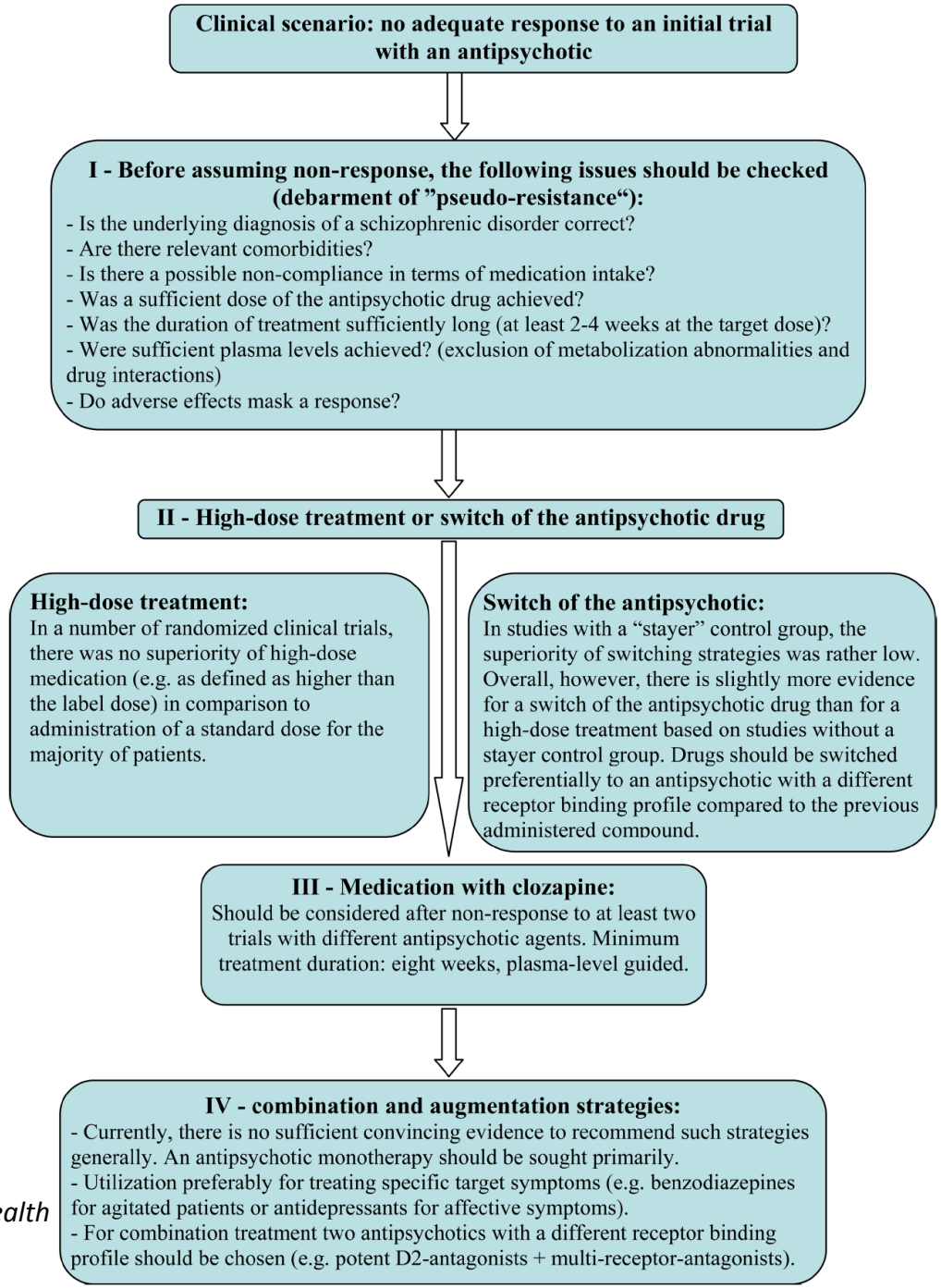
Markus Dold,[1] Stefan Leucht[1,2]

[1]Department of Psychiatry and Psychotherapy, Technical University Munich, Klinikum rechts der Isar, Munich, Germany; [2]Department of Psychiatry, University of Oxford, Oxford, UK

**ABSTRACT**

A significant number of patients with schizophrenia do not respond adequately to an initial antipsychotic trial. As first step within a treatment algorithm for therapy-refractory schizophrenia 'pseudoresistance' should be ruled out (eg, re-evaluation of the diagnosis, comorbidities, compliance and adherence in terms of medication intake, adequate dose and treatment duration, and achievement of sufficient plasma levels). In case of treatment resistance, two strategies that are often used in clinical routine care contain dose increase of the current administered antipsychotic drug (dose escalation, high-dose treatment) and switch to another, new antipsychotic. Although the response rates for both options are generally rather low, we see from the evidence-based perspective a slight advantage of the switching strategy (preferably to an antipsychotic with a different receptor-binding profile) compared to a high-dose treatment. After treatment failures with at least two different antipsychotic drugs, a monotherapy with clozapine is considered to be the treatment option of first choice. At present, pharmacological combination and augmentation strategies cannot be regarded as a generally recommendable evidence-based treatment method. Antipsychotic monotherapy should be preferably sought. In case of combination treatment, it appears more appropriate to combine preferentially two antipsychotics with different receptor-binding profiles. Augmentation of antipsychotics with other agents should be used primarily to treat specific target symptoms.

Dold et Leucht, *Evid Based Mental Health* May 2014 Vol 17 No 2




Dold et Leucht, *Evid Based Mental Health* May 2014 Vol 17 No 2

# A « pseudo-resistance » ?

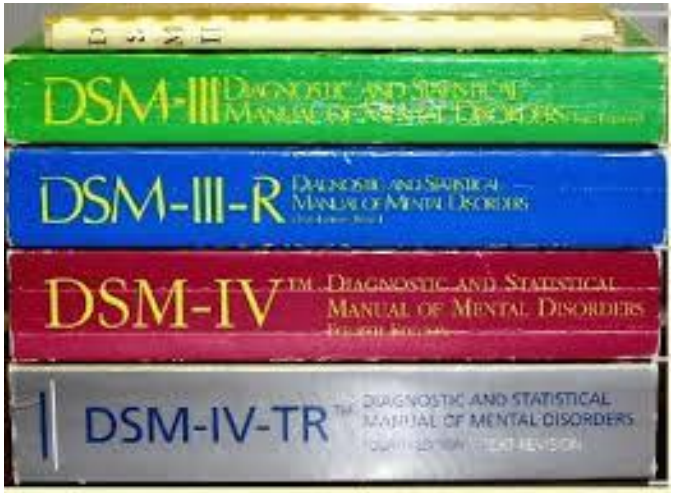
1 – Diagnosis ?

2 – Treatment ?

3 – Non-adherence ?

# What about the diagnosis ?

- **Severe personnality disorders**
- **Affective disorders with psychotic characteristics**
- **Neurological causes**
  - brain tumors
  - encephalopathy
- **Comorbidity**
  - OCD
  - Affective disorders




Dold et Leucht, *Evid Based Mental Health* May 2014 Vol 17 No 2

# Treatment ?

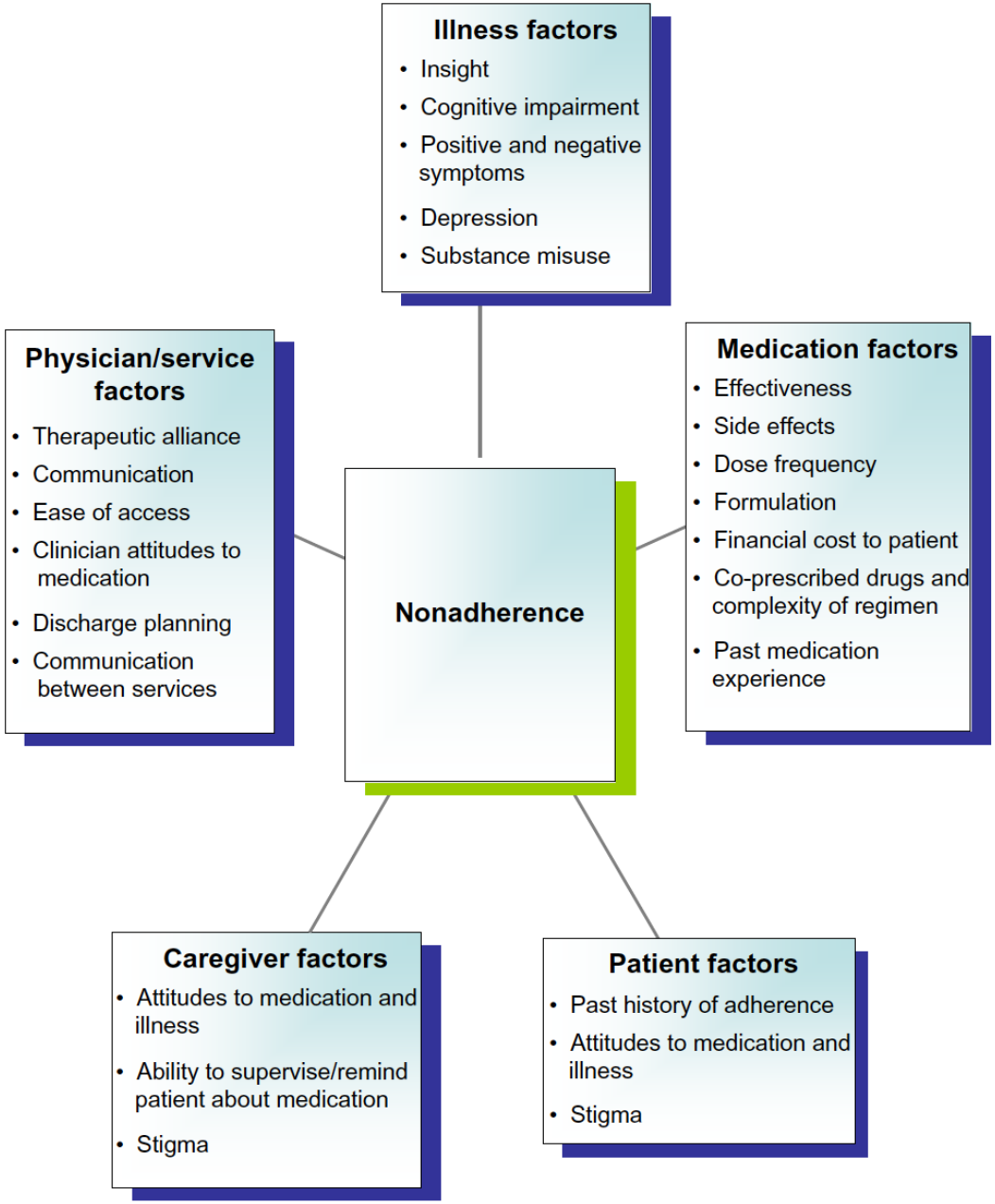
- *At optimum doses and over sufficiently long period*
- Therapeutic drug monitoring +++
  - 44% subtherapeutic plasma level,
  - 1/3 of patients identified Treatment Resistant
- How long ?
  - 2-8 weeks
  - 1st week response is predictive.

**Table 1** Recommended doses of selected first-generation and second-generation antipsychotic drugs for the pharmacological treatment of schizophrenia and related disorders based on an international consensus survey[13]

| Drug | Recommended starting dose (in mg/day) | Recommended target dose (in mg/day) | Recommended maximum dose (in mg/day) |
|---|---|---|---|
| First-generation antipsychotic drugs | | | |
| | 100 | 300–600 | 800 |
| Chlorpromazine | | | |
| Flupentixol | 3 | 5–12 | 18 |
| Fluphenazine | 3 | 5–15 | 20 |
| Haloperidol | 3 | 5–10 | 20 |
| Perphenazine | 8 | 12–24 | 42 |
| | 5 | 10–20 | 35 |
| Trifluoperazine | | | |
| Second-generation antipsychotic drugs | | | |
| Amisulpride | 100 | 400–800 | 1000 |
| Aripiprazole | 10 | 15–30 | 30 |
| Clozapine | 25 | 200–500 | 800 |
| Olanzapine | 5 | 10–20 | 30 |
| Paliperidone | 3 | 6–9 | 12 |
| Quetiapine | 100 | 400–800 | 1000 |
| Risperidone | 2 | 4–6 | 8,5 |
| Ziprasidone | 40 | 120–160 | 200 |
| Zotepine | 50 | 100–300 | 400 |

Gardner et al., Am J Psychiatry; *2010; 167:686–693;* Dold et Leucht, *Evid Based Mental Health* May 2014 Vol 17 No 2; McCutcheon et al., *J. of Psychopharmacology*, June 2015; Agid et al., *Arch Gen Psychiatry* 2003;60:1228–35

# Non adherence ?




from Haddad et al., *Patient Related Outcome Measures*. 2014 Jun;43.

# Clozapine, the gold standard

- **Cloza vs First Generation Antipsychotics (FGA)**:

  => cloza > FGA (relapse rates and repeated hospitalisations) (Meltzer et al., 2008).

- **Cloza vs Second Generation Antipsychotics (SGA)**:

  - Cloza > all SGA except olanzapine (OLZ) (Phase II CATIE).

  - Cloza > OLZ on suicidal behaviors (Intersept: Meltzer et al., 2003)

  - „ pro-cognitive “ effects of OLZ > cloza (anticholinergic properties).

  - Tolerance: a limitation of its use (weight, metabolic disturbances, agranulocytosis, sedation).

# When Clozapine fails …

## Ultra-resistant schizophrenia

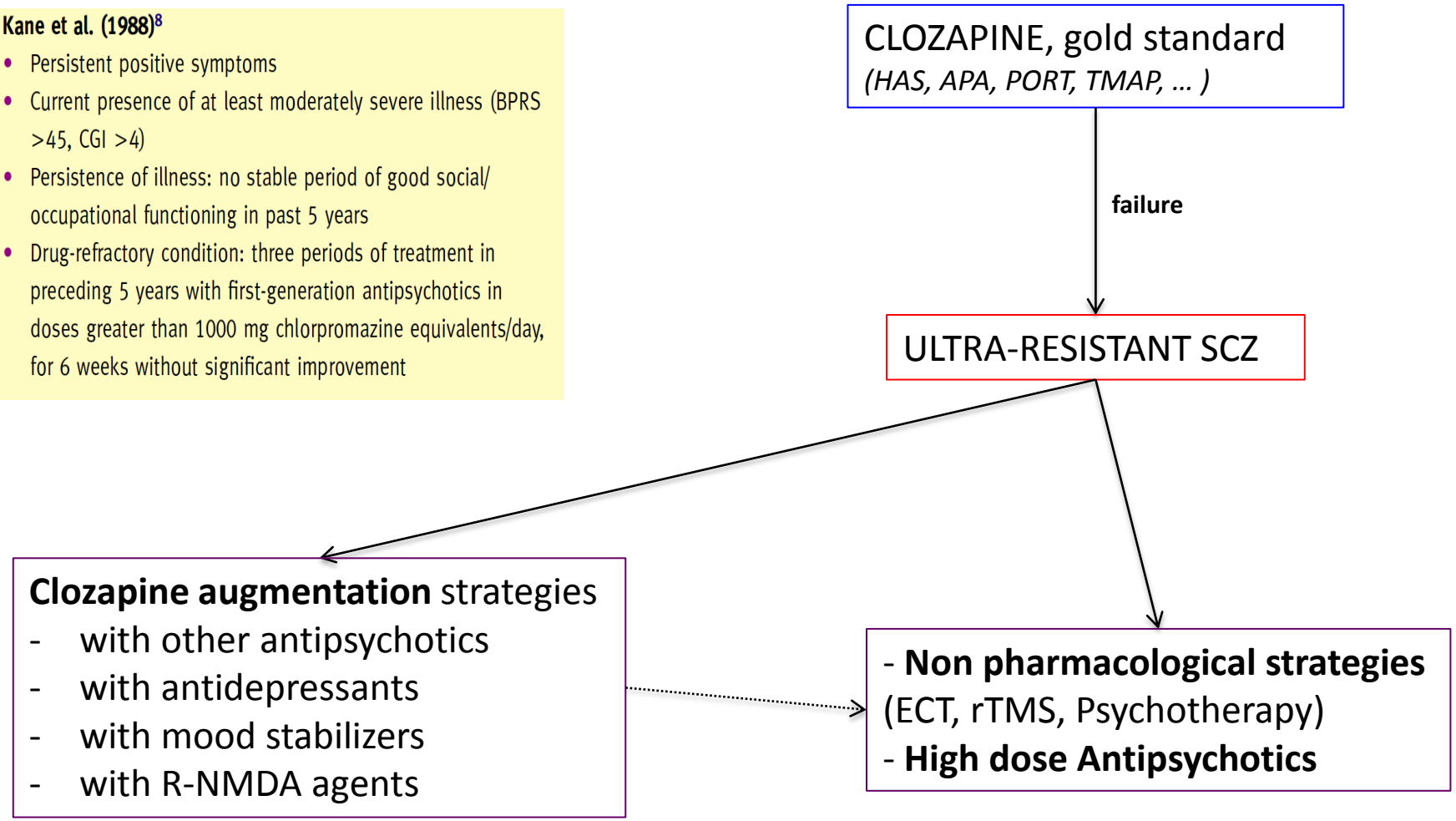
(Mouaffak et al., 2006)

BPRS improvement of < 20% despite a trial with clozapine for ≥ 8 weeks and plasma levels > 350 μg/L, no stable period of good social and/or occupational functioning for ≥ 5 years, Global Assessment of Functioning (GAF) ≤ 40, BPRS total score ≥ 45, CGI score ≥ 4, and a score of ≥ 4 on 2 of 4 positive symptom items.

# ALGORITHM FOR TREATMENT RESISTANT SCHIZOPHRENIA

**Kane et al. (1988)[8]**

- Persistent positive symptoms
- Current presence of at least moderately severe illness (BPRS >45, CGI >4)
- Persistence of illness: no stable period of good social/ occupational functioning in past 5 years
- Drug-refractory condition: three periods of treatment in preceding 5 years with first-generation antipsychotics in doses greater than 1000 mg chlorpromazine equivalents/day, for 6 weeks without significant improvement




*Barnes et Dursun, Psychiatry, 2005; American Psychiatric Association, 2010; Mcilwain, Neuropsychiatr Dis Treat, 2011; Mouaffak et al., Clin Neuropharmacol, 2006*

# Clozapine augmentation strategies

Review

# Augmentation strategies in partial responder and/or treatment-resistant schizophrenia patients treated with clozapine

Maria Rosaria A Muscatello[†], Antonio Bruno, Pasquale De Fazio, Cristina Segura-Garcia, Gianluca Pandolfo & Rocco Zoccali

[†]*University of Messina, Department of Neurosciences, Messina, Italy*

*Expert Opin. Pharmacother.* (2014) 15(16):2329-2345

# Augmentation with antipsychotics

| Augmentation strategy | Number of studies | Positive (+) or negative (−) outcome | Risks | Benefits |
|---|---|---|---|---|
| *Antipsychotics* | | | | |
| Risperidone | 11 | + + + + + + − − − − − | Cognition worsening;<br>↑ Prolactin<br>↑ Glucose PL | |
| Ziprasidone | 2 | + + | ↑ QTc interval | |
| Aripiprazole | 6 | + + + + + − | | ↓ Negative symptoms;<br>↓ Metabolic side effects |
| Amisulpride | 5 | + + + + + | Bradykinesia<br>Akathisia<br>Tremor<br>↑ Prolactin | |
| Sulpiride | 1 | + | ↑ Prolactin | |

- No current consensus regarding this strategy
- Promote pharmacologically synergistic associations
- Tolerance monitoring ++

Muscatello et al., *Expert Opin. Pharmacother.* (2014) 15(16):2329-2345;
Porcelli et al., *European Neuropsychopharmacology* (2012) 22, 165–182

# Augmentation with mood stabilizers

| Augmentation strategy | Number of studies | Positive (+) or negative (−) outcome | Risks | Benefits |
|---|---|---|---|---|
| *Mood stabilizers/anticonvulsants* | | | | |
| Lamotrigine | 6 | + + + − − − | | |
| Topiramate | 3 | + − − | Asthenia<br>Sedation | |
| Lithium | 3 | + + − | Hypersalivation<br>Orthostatic dysregulation<br>Oral dyskinesia<br>Weight gain | |
| Divalproex sodium | 1 | + | | ↓ Anxiety<br>↓ Depressive symptoms |

- Interisting in clozapine treated patients with high epileptic risk,
- Schizo-affective disorder,
- Favor valproate, take care of lithium (tolerance).

Muscatello et al., *Expert Opin. Pharmacother.* (2014) 15(16):2329-2345;
Porcelli et al., *European Neuropsychopharmacology* (2012) 22, 165–182

# Augmentation with antidepressant

| Augmentation strategy | Number of studies | Positive (+) or negative (−) outcome | Risks | Benefits |
|---|---|---|---|---|
| *Antidepressants* | | | | |
| Fluoxetine | 2 | − − | ↑ CLZ PL | |
| Fluvoxamine | 3 | + + + | ↑ CLZ PL | ↓ Metabolic side effects |
| Mirtazapine | 3 | + + − | Weight gain | ↓ Negative symptoms; Improvement of cognition |

- Comorbid forms (depression, anxiety, OCD),
- Pharmacokinetic effects (inhibiting CYP1A2) with fluoxetine and fluvoxamine (↑ CLZ ↓norCLZ).

Muscatello et al., *Expert Opin. Pharmacother.* (2014) 15(16):2329-2345;
Porcelli et al., *European Neuropsychopharmacology* (2012) 22, 165–182

# Augmentation with other agents

| Augmentation strategy | Number of studies | Positive (+) or negative (−) outcome | Risks | Benefits |
|---|---|---|---|---|
| *Other agents* | | | | |
| Glycine | 4 | + + − − | | |
| D-cycloserine | 2 | − − | Negative symptoms worsening | |
| D-serine | 1 | − | | |
| Ampakine CX-516 | 2 | + − | Hypertension | |
| N-methylglycine | 1 | − | | |
| Modafinil | 1 | − | Worsening of psychosis | |
| Memantine | 1 | + | | |
| Mazindol | 1 | + | | |
| E-EPA | 3 | + + − | Diarrhea<br>Nausea | |

- Agent involved in glutamatergic transmission (glycine, D-serine, D-cycloserine, ampakine CX516, memantine, N-methylglycine), based on R-NMDA hypofunctionning hypothesis.

Muscatello et al., *Expert Opin. Pharmacother.* (2014) 15(16):2329-2345;
Porcelli et al., *European Neuropsychopharmacology* (2012) 22, 165–182

# Use of high dose olanzapine in Treatment Resistant Schizophrenia

# High dose olanzapine in TRS

- Since the late 1990s,
  - at doses between 25-45 mg/d -> as effective as clozapine (100-600mg/d) (Tollefson et al., 2001; Bitter et al., 2004; Meltzer et al., 2008)
  - interesting for cognitive deficit and hallucinations, better social functionning (Qadri et al., 2006 ; Reich, 2009)
  - Good tolerance even at very high doses (Batail et al., 2012; Batail et al., 2014)

$\Rightarrow$ a worthwhile alternative for clozapine-resistant or intolerant patients (Baldacchino et al., 1998; Dursun et al., 1999; Martin et al., 1997; Rodriguez-Perez et al., 2002)

**Open Journal of Psychiatry, 2012, 2, 269-271** **OJPsych**
doi:10.4236/ojpsych.2012.24037 Published Online October 2012 (http://www.SciRP.org/journal/ojpsych/)

# Very-high-dose olanzapine for treatment-resistant schizophrenia

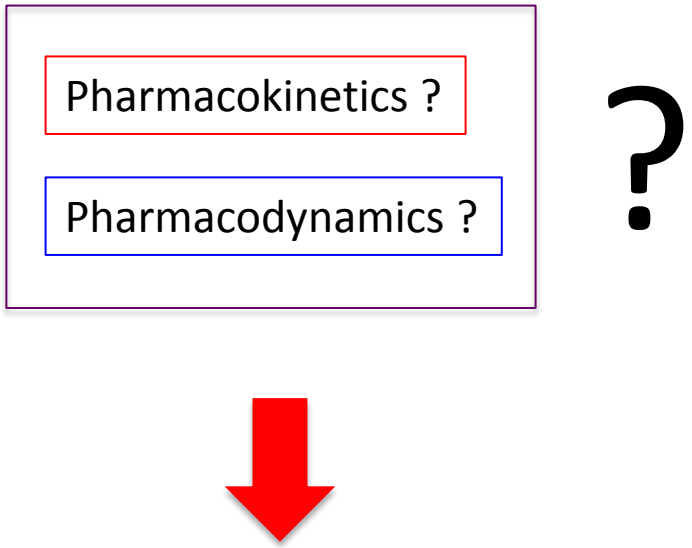
**Jean-Marie Batail[1,2*], Sophie Bleher[1], Clément Lozachmeur[1,2], Gabriel Robert[1,2], Bruno Millet[1,2], Dominique Drapier[1,2]**

## ABSTRACT

**Treatment-resistant schizophrenia has an extremely negative impact on mental health and social life. If clozapine, the gold standard treatment, fails, there are very few options left. The literature suggests that high-dose olanzapine (20 - 60 mg/day) is a possible alternative. We report two cases in which very high doses of olanzapine were administered, with significant clinical improvements above 60 mg/day. Clinical, metabolic and cardiac tolerance was good. This report highlights the usefulness of very-high-dose olanzapine in treatment-resistant schizophrenia. The main hypotheses concerning the psychopharmacological mechanisms of very-high-dose olanzapine are discussed.**

# A STUDY ON PHARMACOKINETICS OF HIGH DOSE OLANZAPINE IN PATIENT SUFFERING FROM SCHIZOPHRENIA

Question of the psychopharmacological mechanism behind the therapeutic response at such high doses ?




Comparison of pharmacokinetics of olanzapine at both conventional and high doses.

Schizophrenia Research 159 (2014) 411–414

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

# Use of very-high-dose olanzapine in treatment-resistant schizophrenia

J.-M. Batail [a,b,*], B. Langrée [c,e,f], G. Robert [a,b], S. Bleher [a,b], M.-C. Verdier [d,e,f], E. Bellissant [d,e,f], B. Millet [a,b], D. Drapier [a,b]

**Table 1**
Clinical characteristics of the whole sample.

| Variable | Sample |
|---|---|
| Age (years) ($N = 50$) | 35.42 ± 1.48 |
| Sex (male) ($N = 50$) | 30 (60%) |
| Tobacco | |
| Smokers ($n = 46$) | 31 (67%) |
| Cigarettes/day ($n = 46$) | 10.91 ± 1.55 |
| PANSS ($n = 41$) | |
| Positive score | 14.23 ± 0.94 |
| Negative score | 17.28 ± 0.95 |
| Psychopathology score | 30.42 ± 1.65 |
| Total score | 61.93 ± 3.12 |
| ESRS ($n = 42$) | |
| Dyskinesia subscale | 1 (2.38%) |
| Dystonia subscale | 1 (2.38%) |
| Parkinsonism subscale | 5 (11.91%) |
| Akathisia subscale | 4 (9.52%) |
| UKU ($n = 42$) | |
| Psychic subscale | 3.21 ± 0.31/27 |
| Neurological subscale | 0.27 ± 0.10/24 |
| Neurovegetative subscale | 1.02 ± 0.22/33 |
| Others | 1.42 ± 0.31/57 |
| CGI | |
| Severity scale ($n = 41$) | 4.14 ± 0.22 |
| Improvement scale ($n = 37$) | 25 (68%) |

Schizophrenia Research 159 (2014) 411–414

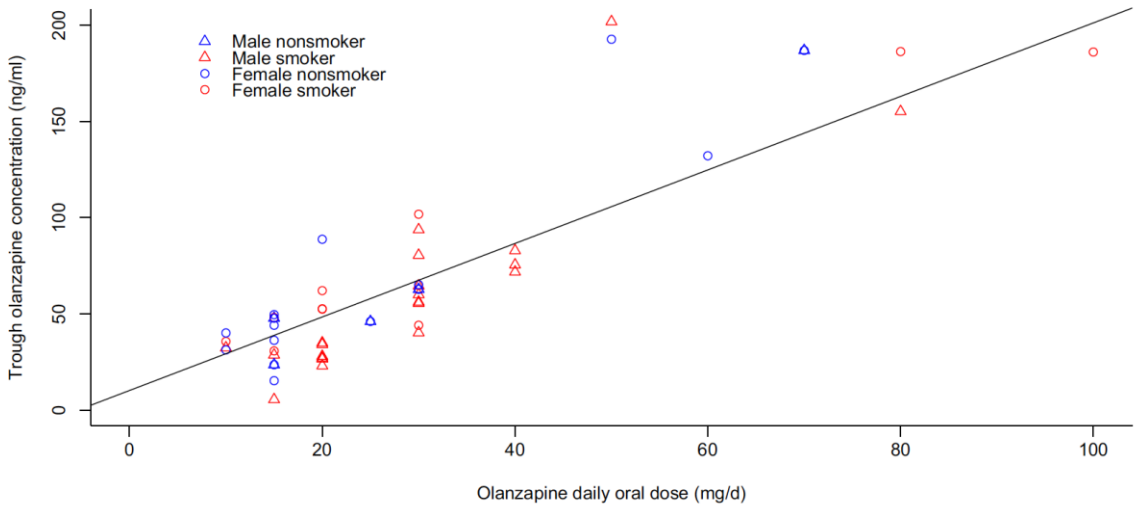
Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

# Use of very-high-dose olanzapine in treatment-resistant schizophrenia

J.-M. Batail [a,b,*], B. Langrée [c,e,f], G. Robert [a,b], S. Bleher [a,b], M.-C. Verdier [d,e,f], E. Bellissant [d,e,f], B. Millet [a,b], D. Drapier [a,b]




- Linear dose – concentration relationship ($r = 0.83$, $p < 0.001$)
- Good concentration – tolerance relationship

⇒ Pharmacodynamic characteristic of response to high dose olanzapine ?

# To conclude

- Key points:
  - lack of definition
  - screening pseudo-resistance (therapeutic drug monitoring, non adherence, …)
  - pharmacological strategies
- Clozapine, remains the gold standard
  - lack of evidence of pharmacological augmentation strategies
  - High dose olanzapine, a good alternative and experimental paradigm of TRS
- Other alternatives
  - Non pharmacological therapies (neurostimulation, psychotherapy, …)
  - Pharmacological therapies modulating glutamatergic transmission

Euro Global Summit and Medicare Expo on
Psychiatry
July 20-22, 2015 Barcelona, Spain

# Pharmacological Managment of Treatment Resistant Schizophrenia

Jean-Marie Batail - France

21st July 2015

Comportement et Noyaux Gris Centraux

Centre Hospitalier Guillaume RÉGNIER

UNIVERSITÉ DE RENNES 1