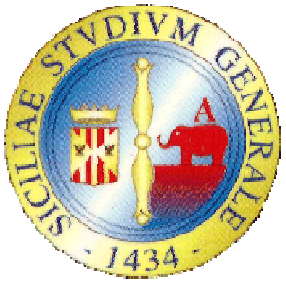

Corso di Laurea Magistrale in Psicologia
Laboratorio di Psicofarmacologia
Università degli Studi di Catania

Uso off-label degli antipsicotici di seconda generazione

Filippo Caraci & Filippo Drago

Uso off-label degli antipsicotici

- Quasi il 50% delle prescrizioni di antipsicotici di seconda generazione e meno del 15% di quelle di antipsicotici di prima generazione sono off-label..
- Gli antipsicotici di prima generazione paradossalmente mantengono ancora indicazioni più ampie dei nuovi antipsicotici pur in assenza di studi controllati sulla tollerabilità di questa classe di farmaci.
- Gli antipsicotici di seconda generazione hanno invece ottenuto dalle autorità regolatorie indicazioni più ristrette in rapporto alle specifiche patologie studiate negli studi controllati
- ***Gli antipsicotici di seconda generazione sono largamente utilizzati per il trattamento dei disturbi di personalità e dei BPSD***

USO OFF-LABEL DEI FARMACI

- Si definisce off-label l'uso nella pratica clinica di farmaci già registrati, ma usati in maniera non conforme a quanto previsto dalla scheda tecnica autorizzata dal Ministero della Salute (prescrizione di farmaci per indicazioni, modalità di somministrazione, dosaggi differenti da quelli indicati nel riassunto delle caratteristiche del prodotto).
- Si tratta di molecole ampiamente conosciute e utilizzate secondo schemi e linee guida ufficiali, ma per le quali nuove evidenze scientifiche suggeriscono un loro razionale uso anche in situazioni cliniche non previste nella scheda tecnica e nel foglietto illustrativo di farmaci autorizzati all'immissione in commercio dal Ministero della Salute o dall'Agenzia Europea di Valutazione dei Medicinali (EMA)

Fondamentali sono i seguenti requisiti:

- assenza di alternative terapeutiche per il paziente;
- documentazione scientifica pubblicata su riviste qualificate e indicizzate;
- consenso del paziente previa informazione dei benefici e dei rischi connessi.

GESTIONE DELLA TERAPIA FARMACOLOGICA

La responsabilità professionale dello psichiatra nella prescrizione di farmaci off-label e dei farmaci originali e generici

Psychiatrist's professional liability for generic, brand, and off-label drug prescription

GIANCARLO NIVOLI[1], LILIANA LORETTU[2]

Nell'ambito del concetto più generale di appropriatezza prescrittiva del farmaco, rivestono particolare interesse alcuni concetti quali:

– *efficacy*, cioè l'efficacia di un farmaco nell'ambito di uno studio clinico sperimentale controllato e randomizzato;
– *effectiveness*, cioè l'efficacia di un farmaco nella realtà clinica e quindi anche un'accettabile tollerabilità nella quotidiana pratica assistenziale;
– *efficiency*, cioè l'efficacia di un farmaco in relazione anche alla farmaco-economia.

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 Current Pharmaceutical Design, 2015, *21*, 3280-3297

Off-Label Prescribing of Antipsychotics in Adults, Children and Elderly Individuals: A Systematic Review of Recent Prescription Trends

Louise Carton[1,2,*], Olivier Cottencin[1,3], Maryse Lapeyre-Mestre[4], Pierre A. Geoffroy[5,6,7], Jonathan Favre[8], Nicolas Simon[9,10], Régis Bordet[2] and Benjamin Rolland[1,2]

OLP in Adult Populations

The rates for OLP of antipsychotics varied from 15% for FGAPs [7] and 19.5% [8] to 61% for SGAPs [9]. The most frequent rates were between 40 and 75% of all AP prescriptions [10-16]. OLP was most frequently identified with SGAPs compared with FGAPs, i.e., 50 vs. 15% in 2004 and 22 vs. 3.6% in 2005 [7, 17]. Similarly, an increased adherence to on-label indications was identified with FGAPs compared with SGAPs (80.8 vs 36.3%) [18]. Among the OLP of SGAPs, quetiapine was consistently the most frequently prescribed drug among adults [8, 19-21], particularly at low-doses [22, 23]. Clozapine was used more frequently for classical indications and was thus the least common antipsychotic prescribed off-label [11, 14, 16].

A pattern of specific off-label indications of antipsychotics was identified in adults, i.e., agitation, mood disorders, anxiety disorders, insomnia, borderline personality disorders, obsessive compulsive disorder, post-traumatic stress disorder and substance-use disorder [8, 10, 18, 20, 23-28]. The most frequent indications were mood disorders, including depression, anxiety disorders, and

Personality disorder 3

Treatment of personality disorder

Anthony W Bateman, John Gunderson, Roger Mulder

The evidence base for the effective treatment of personality disorders is insufficient. Most of the existing evidence on personality disorder is for the treatment of borderline personality disorder, but even this is limited by the small sample sizes and short follow-up in clinical trials, the wide range of core outcome measures used by studies, and poor control of coexisting psychopathology. Psychological or psychosocial intervention is recommended as the primary treatment for borderline personality disorder and pharmacotherapy is only advised as an adjunctive treatment. The amount of research about the underlying, abnormal, psychological or biological processes leading to the manifestation of a disordered personality is increasing, which could lead to more effective interventions. The synergistic or antagonistic interaction of psychotherapies and drugs for treating personality disorder should be studied in conjunction with their mechanisms of change throughout the development of each.

Lancet 2015; 385: 735–43

See Editorial page 664

This is the third in a Series of three papers about personality disorder

Barnet, Enfield, and Haringey Mental Health NHS Trust, London, UK (Prof A W Bateman FRCPsych); **University College London, London, UK** (Prof A W Bateman); **Anna Freud Centre, London, UK**

The two main approaches to the treatment of personality disorder are psychosocial treatment and pharmacotherapy.

Psychosocial intervention is recommended as the primary treatment for borderline personality disorder and other personality disorders

Treatment of personality disorders

- The present American Psychiatric Association guideline states that symptom targeted pharmacotherapy is an important adjunctive treatment.
- This therapy is based on Siever and Davis'23 dimensions of :
- Affective instability (treated with selective serotonin reuptake inhibitor [SSRIs] or monoamine oxidase inhibitors),
- Impulsive aggression (treated with SSRIs or mood stabilisers)
- Cognitive–perceptive disturbances (treated with low dose antipsychotics).

Bateman et al. Lancet 2015

Treatment of personality disorders

- By contrast the UK's NICE guidelines state that drug treatment should generally be avoided, except in a crisis, and then given for no longer than 1 week.

- The World Federation of Societies of Biological Psychiatry guidelines60 stated that moderate evidence exists for antipsychotic drugs being effective for cognitive–perceptual and impulsive– aggressive symptoms, that some evidence exists for SSRIs being effective for emotional dysregulation, and that some evidence exists for mood stabilisers being eff ective for emotional dysregulation and impulsive–aggressive symptoms.

Bateman et al. Lancet 2015

Treatment of personality disorders

- The situation is complicated by the fact that drugs are used very frequently in the treatment of borderline personality disorder despite the scarcity of evidence for their use.
- Zanarini and colleagues reported that 78% of patients with borderline personality disorder were on drugs for more than 75% of the time during a 6 year period. Additionally, 37% of these patients were on three or more drugs. In view of this situation clinicians should be guided towards the drugs with at least some evidence.
- The NICE guidelines explicitly state that if patients have no comorbid illness, efforts should be made to reduce or stop pharmacotherapy.

Bateman et al. Lancet 2015

Panel 3: Recommendations for the use of drugs in borderline personality disorder

- Drugs should not be used as primary therapy for borderline personality disorder
- The time-limited use of drugs can be considered as an adjunct to psychosocial treatment, to manage specific symptoms
- Cautious prescription of drugs that could be lethal in overdose or associated with substance misuse
- The use of drugs can be considered in acute crisis situations but should be withdrawn once the crisis is resolved
- Drugs might have a role when a patient has active comorbid disorders
- If patients have no comorbid illness, efforts should be made to reduce or stop the drug

Adapted from National Health and Medical Research Council (Australia) and National Institute for Health and Care Excellence (UK) guidelines.

Bateman et al. Lancet 2015

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Pharmacological interventions for borderline personality disorder

Jutta Stoffers[2], **Birgit A Völlm**[3], **Gerta Rücker**[4], **Antje Timmer**[5], **Nick Huband**[3], and **Klaus Lieb**[1]

Background—Drugs are widely used in borderline personality disorder (BPD) treatment, chosen because of properties known from other psychiatric disorders ("off-label use"), mostly targeting affective or impulsive symptom clusters.

Selection criteria—Randomised studies comparing drug versus placebo, or drug versus drug(s) in BPD patients. Outcomes included total BPD severity, distinct BPD symptom facets according to DSM-IV criteria, associated psychopathology not specific to BPD, attrition and adverse effects.

Data collection and analysis—Two authors selected trials, assessed quality and extracted data, independently.

Main results—Twenty-eight trials involving a total of 1742 trial participants were included.

The findings were suggestive in supporting the use of second-generation antipsychotics, mood stabilisers, and omega-3 fatty acids, but require replication, since most effect estimates were based on single studies. The long-term use of these drugs has not been assessed.

Adverse event data were scarce, except for olanzapine. There was a possible increase in self-harming behaviour, significant weight gain, sedation and changes in haemogram parameters with olanzapine. A significant decrease in body weight was observed with topiramate treatment. All

Direct drug comparisons comprised two first-generation antipsychotics (loxapine versus chlorpromazine), first-generation antipsychotic against antidepressant (haloperidol versus amitriptyline; haloperidol versus phenelzine sulfate), and second-generation antipsychotic against antidepressant (olanzapine versus fluoxetine). Data indicated better outcomes for phenelzine sulfate but no significant differences in the other comparisons, except olanzapine which showed more weight gain and sedation than fluoxetine. The only trial testing single versus combined drug treatment (olanzapine versus olanzapine plus fluoxetine; fluoxetine versus fluoxetine plus olanzapine) yielded no significant differences in outcomes.

Authors' conclusions—The available evidence indicates some beneficial effects with second-generation antipsychotics, mood stabilisers, and dietary supplementation by omega-3 fatty acids. However, these are mostly based on single study effect estimates. Antidepressants are not widely supported for BPD treatment, but may be helpful in the presence of comorbid conditions. Total BPD severity was not significantly influenced by any drug. No promising results are available for the core BPD symptoms of chronic feelings of emptiness, identity disturbance and abandonment. Conclusions have to be drawn carefully in the light of several limitations of the RCT evidence that constrain applicability to everyday clinical settings (among others, patients' characteristics and duration of interventions and observation periods).

Quetiapine in personality disorders

- A number of open studies have investigated the role of quetiapine in BPD. The control of impulsivity in BPD by quetiapine was assessed and showed promising results with few adverse effects; the adverse effects observed were predominantly sedation and weight gain

- *Several studies have additionally suggested the potential benefit of quetiapine in other features of BPD*, such as affective symptoms and cognitive symptoms (Van den Eynde et al. 2009)

EXPERIMENTAL AND THERAPEUTIC MEDICINE 9: 643-652, 2015

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