A COSA SERVONO I FARMACI? ASPETTATIVE, FALSI MITI, EVIDENZE

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Past President EAMH-ID - European Association on Mental Health in Intellectual Disability
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Dott. Marco Bertelli
Disclosure

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President Elect of the Italian Association for the study of Quality of Life (AISQuV)
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Past President of the European Association for Mental Health in Intellectual Disability (EAMH-ID)
Past Chair of the section Psichiatry of Intellectual Disability of the World Psychiatric Association (WPA-SPID) (2008-2014)

Past member of the working group on Classification of Intellectual and Developmental Disabilities, referring to the International Advisory Group of the World Health Organisation (WHO) on the Revision of ICD-10 – Mental and Behavioural Disorders

Previous collaboration with the following pharmaceutical enterprises:
Farmades
Novartis
Janssen
Eli Lilly
Lundbeck
FB Health - Neuraxpharm

PROBLEMATICHE EMERGENTI

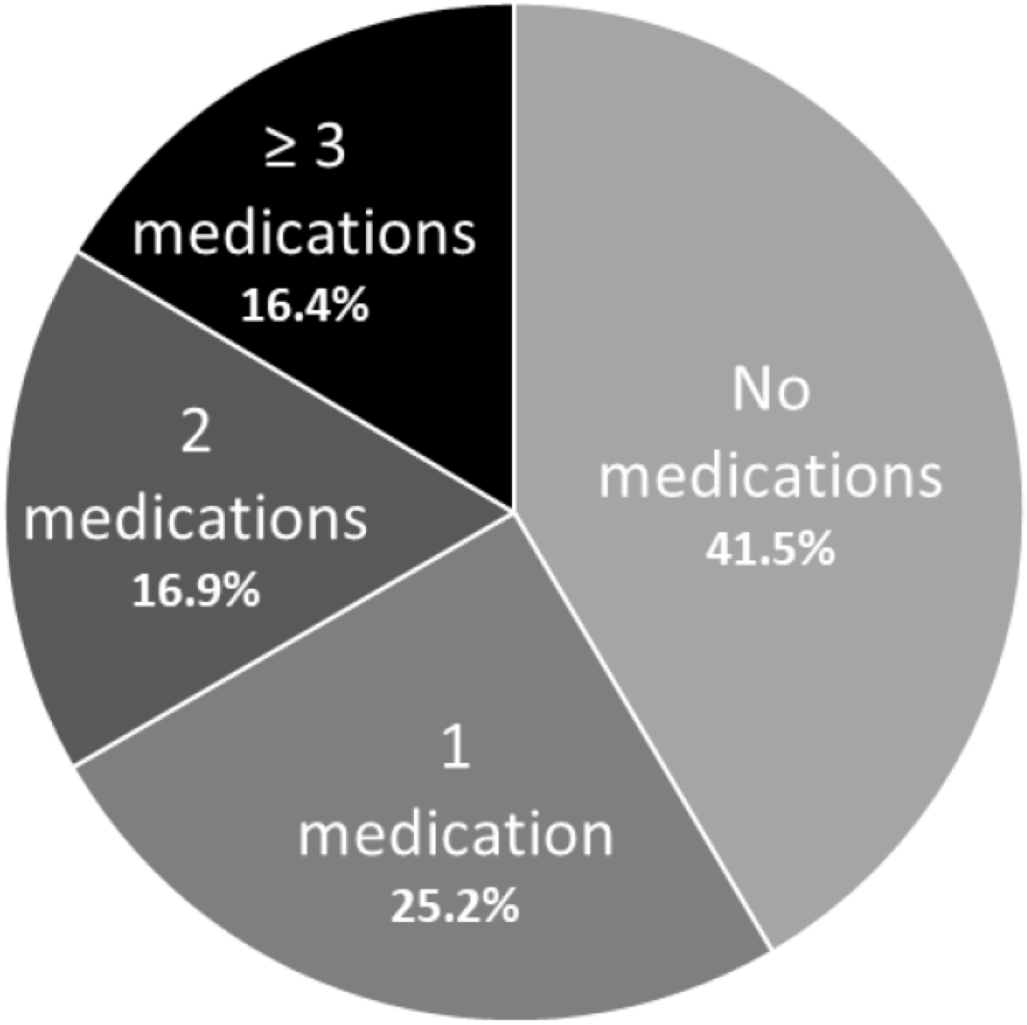
- Ampio uso
  - quantità e durata
- mancanza di ricerca
- indicazioni
- difficoltà diagnostiche e fenomenica dei disturbi psichiatrici
- uso off-label
- sicurezza e tollerabilità
- misure di esito
- uso interdisciplinare
- aspetti etici

TASSO DI FARMACOTERAPIA

- 32-89%, più alto negli adolescenti e negli adulti
- 45% degli adulti

Bachmann et al., 2014; Merikangas et al., 2013; Steinhausen & Bisgaard, 2014; de Kuijper et al., 2010; Doan et al., 2013; Holden & Gitlesen, 2004; Stolker et al., 2002; Langworthy-Lam et al., 2002; Deb et al., 2015

PSYCHOTROPIC MEDICATION IN ADOLESCENTS AND ADULTS WITH ASD



Fusar-Poli L, Brondino N, Rocchetti M, et al. Prevalence and predictors of psychotropic medication use in adolescents and adults with autism spectrum disorder in Italy: A cross-sectional study. Psychiatry Res. 2019 Jun;276:203-209.

POLIFARMACOTERAPIA

Poli-Prescrizione

Non è raro per le persone con DI assumere molti farmaci per una varietà di disturbi e malattie. In questo documento tuttavia il termine poli-prescrizione fa riferimento all'utilizzo di più farmaci per una stessa specifica indicazione, cioè un problema di comportamento

Evidenze a Supporto della Poli-Prescrizione

- mancano studi sull'efficacia e la sicurezza delle combinazioni farmacologiche per la gestione dei PC nella DI
- non è possibile offrire alcuna linea-guida
- alcuni studi osservazionali sembrano tuttavia indicare che la riduzione della poli-prescrizione può non solo migliorare il comportamento, ma anche la qualità della vita della persona
- attenzione effetti indesiderati da interferenze farmacocinetiche

POLIFARMACOTERAPIA: EFFETTO DEPRESSOGENO

Metanalisi (CSS USA 2005-2014 N=26192, età media=46,2 aa)

- uso di farmaci con depressione come EI = 37,2%
- anti-ipertensivi, ormoni (modificatori, es. finasteride), ansiolitici, antidolorifici (es. tramadolo o ibuprofene), IPP, antiepilettici, corticosteroidi
- polifarmacoterapia (≥3 farmaci con depressione come EI) = 6,9%
- incremento della prevalenza della depressione associato all'uso di questi farmaci
- ≥3 farmaci 15% vs nessun farmaco 4,7%

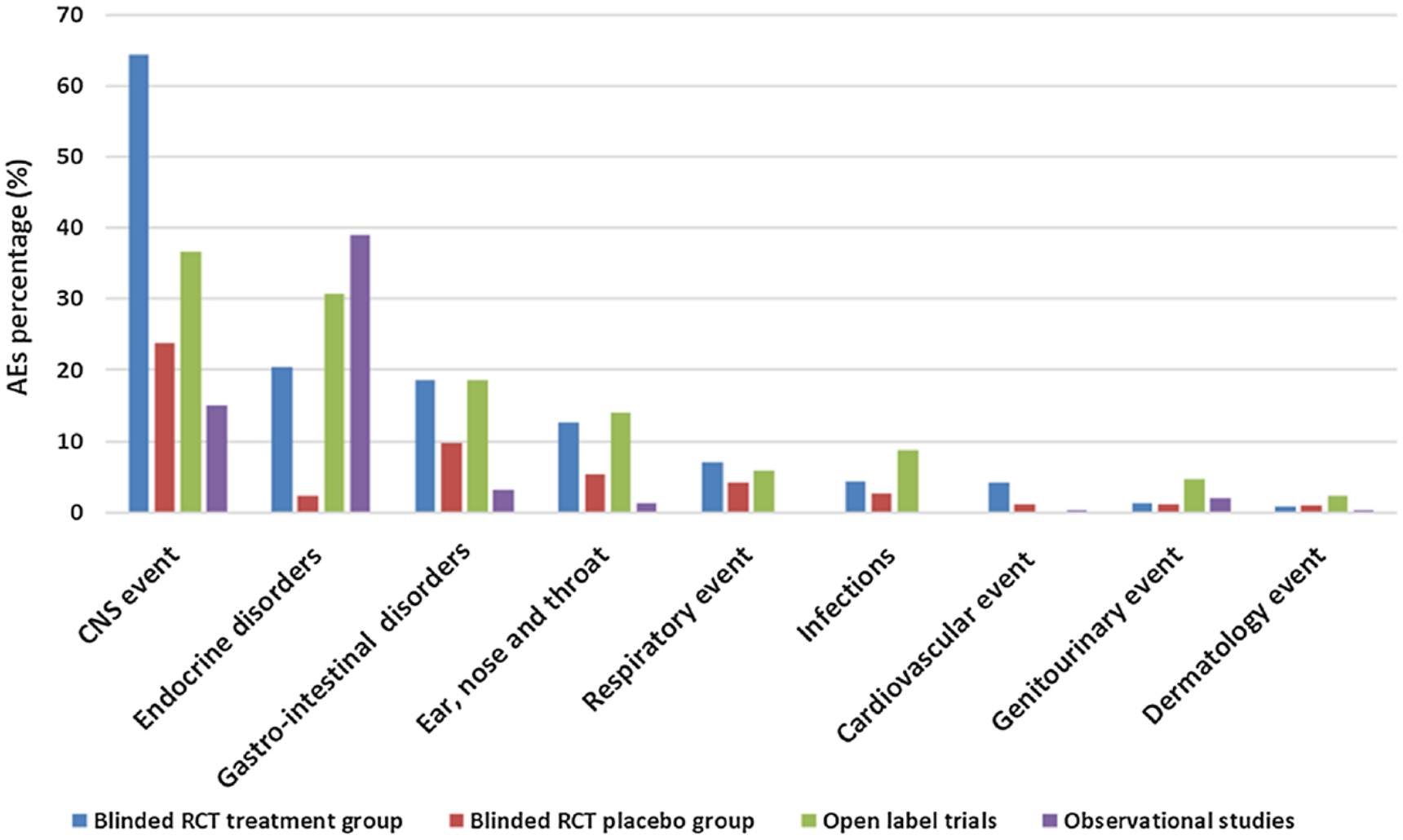
Qato et al. Depression as a Potential Adverse Effect Among Adults in the United States JAMA, 2018

TERAPIE DI LUNGA DURATA

- una volta prescritti, i farmaci tendono a diventare parte integrante del programma d'intervento a lungo termine
- preoccupazione ansiosa degli assistenti e della conseguente riluttanza dei medici generici a modificare un trattamento che viene riferito, più o meno impropriamente, come efficace
- dopo mesi o anni di assunzione, i tentativi di sospensione vanno a buon fine solo in un numero limitato di casi

Esbensen et al., 2009; Ahmed et al., 2000; Bertelli, Vannucchi e Persico, in press

ADVERSE EVENTS OF ANTIPSYCHOTICS IN ASD



Alfageh BH, Wang Z, Mongkhon P, Besag FMC, Alhawassi TM, Brauer R, Wong ICK. Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Paediatr Drugs. 2019; Jun;21(3):153-167.

ADVERSE EVENTS OF ANTIPSYCHOTICS IN ASD

CNS

1) appetite increase
2) sedation
3) somnolence
4) headache
5) Extrapyramidal symptoms (tremor, akathisia and tardive dyskinesia)

Some AEs were infrequent but potentially serious: seizure, intentional self-injury and suicidal ideation

Endocrine

1) weight gain (mean of 1.4 kg vs placebo)
2) hyperprolactinemia (mean of 17.7 ng/ml vs placebo; n.r. 1-18 M, 2-29 F)
3) hyperglycemia
4) hyperleptinemia
5) increased insulin resistance

Alfageh BH, Wang Z, Mongkhon P, Besag FMC, Alhawassi TM, Brauer R, Wong ICK. Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Paediatr Drugs. 2019; Jun;21(3):153-167.

REVIEW

Stopping, rationalising or optimising antipsychotic drug treatment in people with intellectual disability and/or autism

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- Antipsychotic medication is often prescribed to adults with intellectual disability (ID) and/or autism to manage behaviour that challenges despite little research evidence that antipsychotics are effective.
- The STOMP (Stopping Overuse of Medication in People with Learning Disabilities and/or autism) campaign is aimed at reducing inappropriate prescribing of antipsychotic medication for people with ID and/or autism.
- There is an absence of robust evidence on the most effective way to reduce or stop antipsychotic medication.
- Withdrawing medication requires a multidisciplinary approach, consideration of comorbidity and the involvement of patients and their carers.

Intellectual disability (ID; also known as learning disability) is characterised by significant impairment of both cognitive functioning and adaptive behaviours, and an onset in early childhood. People with ID experience a different pattern of morbidity to the general population and die considerably younger than their counterparts without ID.[1] Autism is a neurodevelopmental disorder characterised by troubles with social interaction and communication, and by restricted and repetitive behaviour. In both conditions, complex mental and physical health problems, as well as social issues, are common and are associated with communication difficulties that can result in maladaptive behavioural patterns (often referred to as 'behaviour that challenges'). Ideally, all people presenting with behaviour that challenges should be assessed by a specialist multidisciplinary team (comprising psychiatrists, psychologists, speech and language therapists, occupational therapists) to develop an understanding of the behaviour and an appropriate support plan with tailored treatment strategies and specialist follow-up.[2] Non-pharmacological interventions for challenging behaviour, such as positive behavioural support or cognitive–behavioural therapy and manipulation of environmental triggers, are preferred to psychotropic medication. However, antipsychotic medication is often prescribed to adults with ID and/or autism to manage behaviour that challenges in the absence of severe mental illness, despite there being little research evidence that antipsychotics are effective in this context.[3]

There are complexities in prescribing, dispensing and administering psychotropic medication for adults with ID and/or autism, and a significant proportion will lack capacity to consent to treatment.[4] There is widespread multimorbidity and polypharmacy, increasing the potential for drug–disease and drug–drug interactions. In addition, people with ID and/or autism tend to be more sensitive to adverse drug effects and have atypical responses to drug treatment. A national report that highlighted concerns related to overuse of psychotropic medication in people with ID and/or autism was followed by data from population-based studies describing the scale of psychotropic prescribing in this group of people, a national guideline on assessment and management of behaviour that challenges, a National Health Service (NHS) quality improvement report on optimising the use of medicines and the national Stopping Overuse of Medication in People with Learning Disabilities and/or autism (STOMP) campaign.[2,5–9]

Targeting antipsychotic use

The STOMP campaign is part of the NHS England 'call to action' aimed at reducing inappropriate psychotropic prescribing for people with ID and/or autism. Although it has achieved widespread publicity and support from professional and lay groups, the programme has been limited by a lack of evidence-based advice for clinicians, patients and carers, on an approach to antipsychotic medication reduction. The National Institute for Health and Care Excellence guideline on interventions for people with

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EVIDENZE SCIENTIFICHE

- evidenze di alta qualità sporadiche
- evidenze riferite più a casi singoli o a serie di casi che a RCT
- mancanza di studi che confrontino direttamente farmaci diversi rispetto a sintomi (o comportamenti problema) specifici

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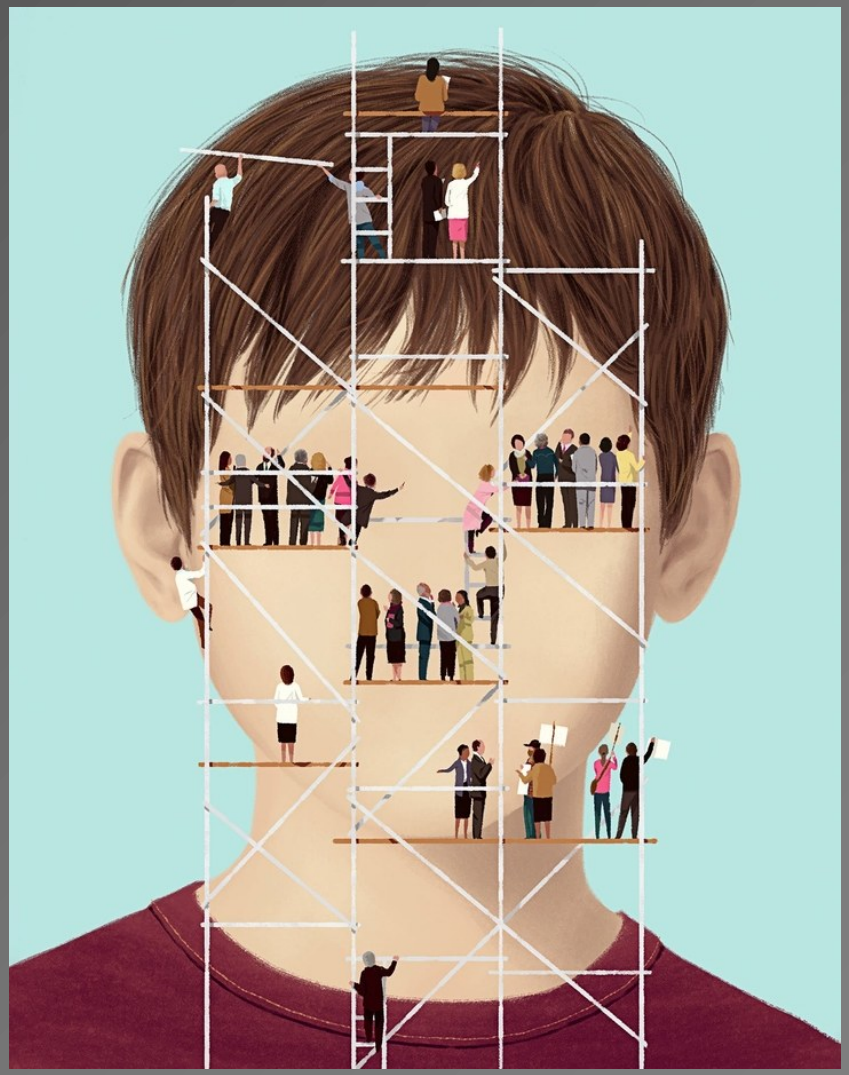


INDICAZIONI

- valutazione e diagnosi
- carenza di linee-guida e letteratura
- mancanza di formazione / capacità tecnica
- Coordinare gli interventi psicofarmacologici con quelli psicoterapeutici, sociali ed educativi

NO EVIDENCE FOR TREATMENT OF CORE SYMPTOMS

- Anticonvulsants
- Chelation
- Exclusion diets
- *Vitamins, minerals and dietary supplements (including omega-3 fatty acids)*
- Drugs specifically designed for cognitive functioning
- Oxytocin
- Secretin
- Testosterone regulation
- Hyperbaric oxygen
- Antipsychotic medication
- Antidepressant medication

USO DELLA FARMACOTERAPIA

Prevalentemente per gestire problemi comportamentali co-occorrenti

- aggressività
- irritabilità
- auto-lesività
- iperattività
- impulsività
- disturbi del sonno
- comportamenti ripetitivi

NO CLEAR EVIDENCE FOR TREATMENT OF PBs IN ID

- the role in aggression of neurotransmitters (serotonin, dopamine and GABA) is no longer as clear as it once appeared
- predictions cannot be made with confidence about drug effects on aggression
- relatively few controlled trials of pharmacotherapy for aggression in people with ID, or, indeed, in the general population
- outcomes have largely been negative

Willner P. The neurobiology of aggression: implications for the pharmacotherapy of aggressive challenging behaviour by people with intellectual disabilities. J Intellect Disabil Res. 2015 Jan;59(1):82-92.

Treatment studies using the early intensive behavioral interventions.

Author(s)	Diagnosis	Number of participants	Age	Target behavior	Treatment(s)
Arnold et al. (2003)	Autism	94	5–17 years old	Aggression	Risperidone
Braithwaite and Richdale (2000)	Autism	1	7 years old	Aggression	Extinction, functional communication
Davis et al. (2013)	Autism	1	Child	Aggression	Functional analysis, weighted vest
Falcomata et al. (2012)	Asperger's syndrome, Autism	2	8 years old	Aggression	Functional communication training, chained schedules of reinforcement, replacement behavior
Fisher et al. (1998)	Autism, intellectual disability (ID)	2	7, 15 years old	Property destruction	Experimental functional analysis, reinforcement of replacement behavior
Foxx and Garito (2007)	Autism	1	12 years old	Aggression, dangerous disruptive behavior	Reinforcement, tokens, choice making, contingent exercise, overcorrection
Foxx and Meindl, 2007	Autism	1	13 years old	Aggression, property destruction	Reinforcement, tokens, choice making, response cost, overcorrection, physical restraint
Fulton et al. (2014)	Autism, PDD-NOS	38	3–5 years old	Aggression, tantrums	Experimental functional analysis, reinforcement methods, replacement behavior
Hanley et al. (2014)	Autism	3	3–11 years old	Hitting	Experimental functional assessment, functional communication training, teaching tolerance and compliance to tasks
Hellings et al. (2005)	Pervasive developmental disorders	30	6–20 years old	Aggression, property destruction	Valproate
Hittner (1994)	Autism	1	Adult	Aggression	Imipramine, behavior modification
Kern et al. (1997)	Autism, ID	1	15 years old	Aggression: grabbing clothing of another person, typically around the neck	Experimental functional analysis, gradual delay of reinforcers, mand training communication as replacement behavior
King and Davanzo (1996)	Autism, ID	26	Adults	Aggression	Buspirone
Kuhn et al. (2009)	Autism, ID	1	16 years old	Hitting, kicking, punching, hair pulling	Experimental functional analysis, functional communication training, blocking
Luiselli et al. (2000)	Autism	1	12 years old	Severe aggression resulting in multiple staff injuries	Clomipramine
Lundqvist et al. (2009)	Autism	20	22–57 years old	Self injury, stereotypies, aggression	Music
Marcus et al. (2009)	Autism	218	6–17 years	Tantrums, aggression	Aripiprazole
Matson et al. (2008a,b)	Autism	1	11 years old	Aggression	Differential reinforcement of other behaviors, compliance training, extinction, functional communication
McDougle et al. (1996)	Autism	30	Adults	Aggression	Fluvoxamine
McDougle et al. (2002)	Autism or PDD-NOS	12	8–20 years old	Aggression, property destruction	Ziprasidone
McDouble et al. (1998)	Autism	31	18–43 years old	Aggression	Risperidone
Owen et al. (2009)	Autism	47	6–17 years old	Aggression, tantrums	Aripiprazole
Robertson et al. (2013)	Autism	2	2, 5 years old	Spitting, throwing objects, hitting, kicking, pushing, pulling hair	Experimental functional analysis
Sigafoos and Meikle (1996)	Autism	2	8 years old	Aggression	Replacement behaviors via mands, experimental functional analysis
Silverman et al. (2014)	Autism, PDD-NOS, Asperger's syndrome	128	5–13 years old	Aggression	Atomoxetine, parent training
Troost et al. (2005)	Autism, PDD-NOS, Asperger's syndrome	36	5–17 years old	Aggression, tantrums	Risperidone
Woodward, Groden, Goodwin, and Bodfish (2007)	Autism	8	9–17 years old	Aggression	Dextromethorphan

DRUGS FOR PBs in ASD

Adults

Imipramine
Fluxoxamine
Buspirone
Imipramine
Risperidone

Adolescents (up to 20 yrs)

Valproate
Ziprasidone

Matson JL, Jang J. Treating aggression in persons with autism spectrum disorders: a review. Res Dev Disabil. 2014 Dec;35(12):3386-91.

FARMACI PSICOTROPI NELLE PcDSA: REVISIONE SISTEMATICA

- 47 studi (fino a novembre 2015 con raccolta dati relativa all'intervallo 1976-2012), comprendente >300 000 persone con DSA

- polifarmacoterapia psicotropa rilevata nel 5.6-54.8% (mediana: 26.2%)

- gli antipsicotici sono risultati i farmaci più utilizzati, seguiti dagli antidepressivi

- età avanzata, sesso maschile, disponibilità di assistenza medica associate con tassi più alti di psicofarmacoterapia

- uso prevalente per sintomi non-core, soprattutto CP

Jobski K, Höfer J, Hoffmann F, Bachmann C. Use of psychotropic drugs in patients with autism spectrum disorders: a systematic review. Acta Psychiatr Scand. 2017 Jan;135(1):8-28.

GLI PSICOFARMACI NELLE PcDSI

- Circa il 20-45% delle PcDSI riceve farmaci psicoattivi

- Il 14-30% riceve tali farmaci per la gestione di CP, in assenza di una chiara diagnosi psichiatrica[1]

- L'alta prescrizione di farmaci psicoattivi non è sostenuta da ricerche su efficacia, sicurezza ed impatto sulla qualità di vita[2]

-Circa i 2/3 dei farmaci prescritti sono rappresentati da antipsicotici[3]

- il 20% degli utenti di strutture residenziali[4] ed il 45% dei ricoverati in ospedale[5] ne riceve almeno uno

1. Deb et al., 1994; Clarke et al., 1990
2. Tyrer et al., 2008; Deb, 2007; Aman et al., 2004; McGillivray et al., 2004; Clarke et al., 1990
3. Spreat et al., 1997
4. Brandford, 1994; Holden, 2004
5. Linaker, 1990

MOTIVI DI PRESCRIZIONE DI FARMACI NEI DSI E DSA

N= 4069 adulti

- 50% disturbo psichiatrico (DP)
- 13% comportamenti problema (CP) gravi
- 38% combinazione di DP e CP

- 58% farmaci psicotropi in generale
- 6% antipsicotici tipici
- 39% antipsicotici atipici
- 23% antidepressivi
- 19% stabilizzatori dell'umore
- 16% antiansia
- 1-2% anti-impulsivi, stimolanti e ipnotici

Tsiouris JA et al. Prevalence of psychotropic drug use in adults with intellectual disability: positive and negative findings from a large study. J Autism Dev Disord, 2012; 25 (Epub ahead of print)

PSYCHOTROPIC MEDICATION IN ADOLESCENTS AND ADULTS WITH ASD

N=195		Univariate regressions			Multivariate regression model		
		B	**β**	***p*-value**	**B**	**β**	***p*-value**
Monopharmacotherpay	**Gender (Female)**	-.68	.50	.12			
	Age	.01	1.01	.54			
	Age at diagnosis	***-.47***	***.95***	***.01***	.01	.99	.75
	IQ	***-.02***	***.98***	***<.001***	***-.03***	***.97***	***.007***
	Severity A (Level 1)	***-1.92***	***.15***	***<.001***	-.02	.97	.98
	Severity A (Level 2)	-1.49	.003	.22	-.03	.97	.97
	Severity B (Level 1)	***-2.24***	***.11***	***<.001***	-1.29	.27	.27
	Severity B (Level 2)	***-1.70***	***.18***	***.002***	-1.11	.33	.29
	Residence (Home)	-1.08	.34	.15	1.17	3.24	.25
	Psychiatric comorbidities	***.91***	***2.48***	***.02***	***2.53***	***12.5***	***<.001***
	Epilepsy	***1.77***	***5.85***	***.01***	***1.70***	***5.45***	***.03***
Polypharmacotherapy	**Gender (Female)**	-.58	.56	.14			
	Age	0.02	1.02	.234			
	Age at diagnosis	***-0.07***	***.94***	***<.001***	.03	1.03	.27
	IQ	***-0.04***	***.96***	***<.001***	***-.04***	***.96***	***.003***
	Severity A (Level 1)	***-3.08***	***.06***	***<.001***	1.36	3.91	.26
	Severity A (Level 2)	***-2.04***	***.13***	***<.001***	1.67	5.33	.10
	Severity B (Level 1)	***-3.56***	***.29***	***<.001***	***-3.41***	***.03***	***.004***
	Severity B (Level 2)	***-2.84***	***.06***	***<.001***	***-3.25***	***.04***	***.002***
	Residence (Home)	***-2.22***	***.11***	***.001***	.56	1.75	.55
	Psychiatric comorbidities	-.48	.62	.26	***1.6***	***4.95***	***.007***
	Epilepsy	***2.52***	***12.41***	***<.001***	***2.02***	***7.53***	***.008***

Fusar-Poli L, Brondino N, Rocchetti M, et al. Prevalence and predictors of psychotropic medication use in adolescents and adults with autism spectrum disorder in Italy: A cross-sectional study. Psychiatry Res. 2019 Jun;276:203-209.

PRESCRIZIONE DI ANTIPSICOTICI NELLA PSICHIATRIA DELLA DISABILITÀ INTELLETTIVA

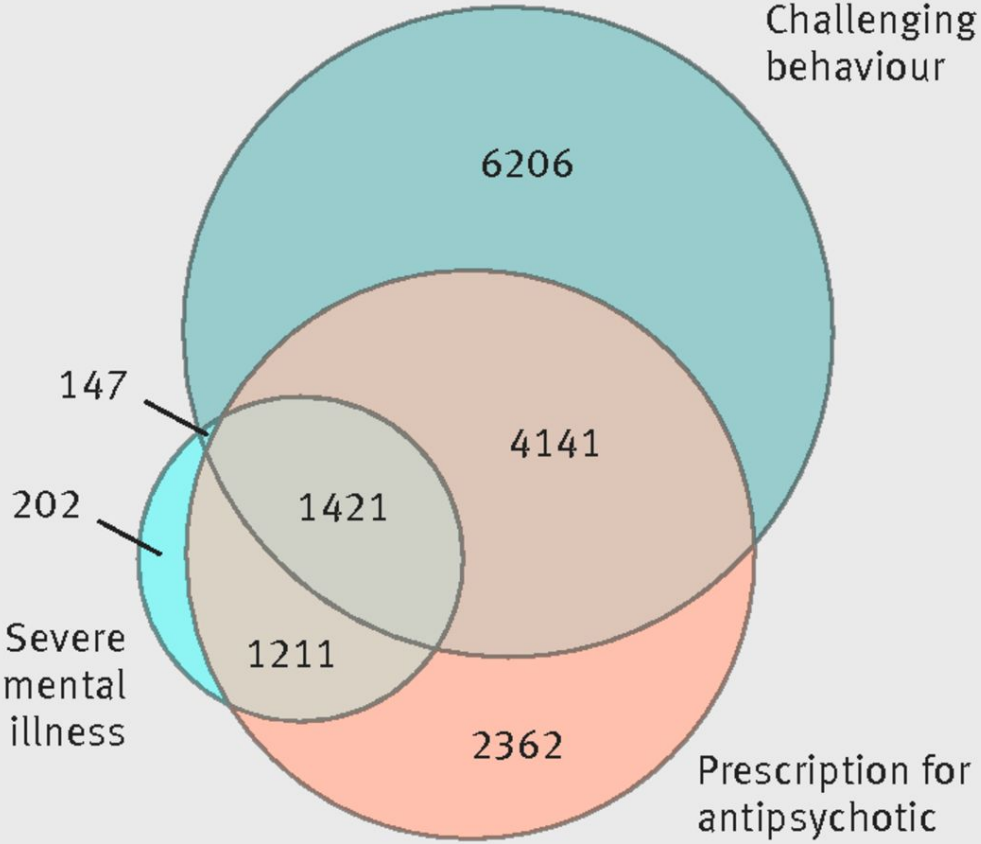
n = 2319
(archivi clinici di 39 servizi di salute mentale del Regno Unito)

- 27% con diagnosi di disturbo psicotico (ICD-10 F20-29)
- 27% con diagnosi di disturbo affettivo (ICD-10 F30-39)
- 6% con ID borderline/lieve, senza diagnosi
- 21% con ID grave/gravissimo, senza diagnosi

- indicazioni più frequenti:
  - comorbidità con disturbo psicotico
  - ansia
  - agitazione
  - vari comportamenti problema
- la prevalenza d'uso di AP per gestire i CP in assenza di diagnosi di disturbo psichiatrico aumenta con la gravità della DI
- 50% delle prescrizioni riguarda le persone con DI grave e gravissima
- elevata adeguatezza agli standard qualitativi delle procedure cliniche (follow-up d'efficacia)
- monitoraggio dei effetti collaterali meno costante

Paton C, Flynn A, Shingleton-Smith A, et al. Nature and quality of antipsychotic prescribing practice in UK psychiatry of intellectual disability services. J Intellect Disabil Res. 2011 Apr 21.

CAUSE DI PRESCRIZIONE DI FARMACI ANTIPSICOTICI



Sheehan R. et al. Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study. BMJ 2015;351:h4326

INCERTEZZA PRESCRITTIVA NEI DNS CON DCC MAGGIORI

Baseline	Fluphenazine 5 mg twice a day	
	Quetiapine 350 mg AM, 350 mg midday, 100 mg at bedtime	
	Lithium 600 mg AM, 450 mg PM	
	Sertraline 50 mg daily	
Month 5	Sertraline discontinued	Antidepressant deemed ineffective because of recurrent behavioral outbursts
Month 8	Medroxyprogesterone acetate depot 150 mg intramuscularly every 3 mo	Initiated after gynecology consult
Month 11	Clonazepam initiated and titrated to 1 mg twice a day	Complaints of anxiety and observed evidence of anxious behaviors
Month 12	Olanzapine 10 mg daily initiated	For continued behavioral outbursts
	Quetiapine tapered to discontinuation	
Month 15	Aripiprazole 10 mg daily initiated	Rapid weight gain noted with olanzapine
	Olanzapine tapered to discontinuation	
Month 16	Escitalopram 5 mg daily initiated, then discontinued within 3 wk	Initiated for observed perseveration. Abrupt increase in agitated behaviors noted.
Month 17	Lamotrigine initiated and titrated gradually to 200 mg daily	For continued dysphoria and anxiety
	Lithium tapered to discontinuation	
Months 18-20	Aripiprazole titrated to 30 mg daily	Attempts to simplify pharmacologic regimen
	Fluphenazine tapered to discontinuation	
	Lamotrigine discontinued	
Month 27	Carbamazepine initiated and titrated to 800 mg daily	Some gradual improvements noted over time

Noel J. Recognition and treatment of mood dysregulation in adults with intellectual disability. Ment Health Clin. 2018 Nov 1;8(6):264-274.

PRESCRIZIONE DI FARMACI OFF-LABEL NELLA PSICHIATRIA DELLA DISABILITÀ INTELLETTIVA

- 67,9% were receiving one or more psychotropic drugs
- 46,4% were receiving at least one off-label psychotropic
- most frequently cited off-label indications were: reduction of aggression, arousal and behavioural disturbance and mood stabilization of affective disturbance
- principal psychotropics involved were atypical antipsychotics and mood stabilizers
- Although in most instances the psychiatrist was aware the drug was being used off-label and had consulted other professionals, in only 6% instances had the patient been informed of the off-label usage, largely because the psychiatrist felt they lacked the capacity to understand the off-label concept
- In most cases the off-label usage had not been documented in the case notes

Haw C, Stubbs J. A survey of off-label prescribing for inpatients with mild intellectual disability and mental illness. J Intellect Disabil Res. 2005 Nov;49(Pt 11):858-64.

ANTIPSYCHOTICS PRESCRIBERS FOR PEOPLE WITH INTELLECTUAL DISABILITIES

n = 178
(patient attending Salford Intellectual Disability Psychiatric Unit, UK)

64% GP on recommendation from secondary care

- 28% unknown
- 8% GP alone or pharmacy

Hannah Griffiths, N. Halder and N. Chauudhry. Antipsychotics prescribing in people with intellectual disabilities: a clinical audit. Advances in Mental Health and Intellectual Disabilities, 2012; 6(4): 215-222.

PROBLEMATICHE EMERGENTI

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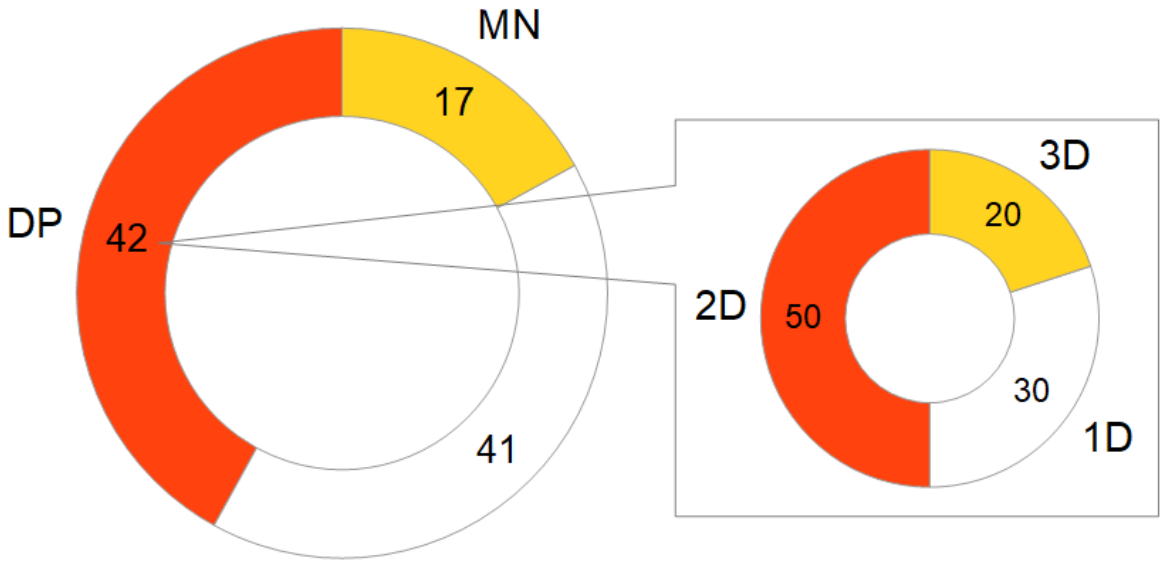
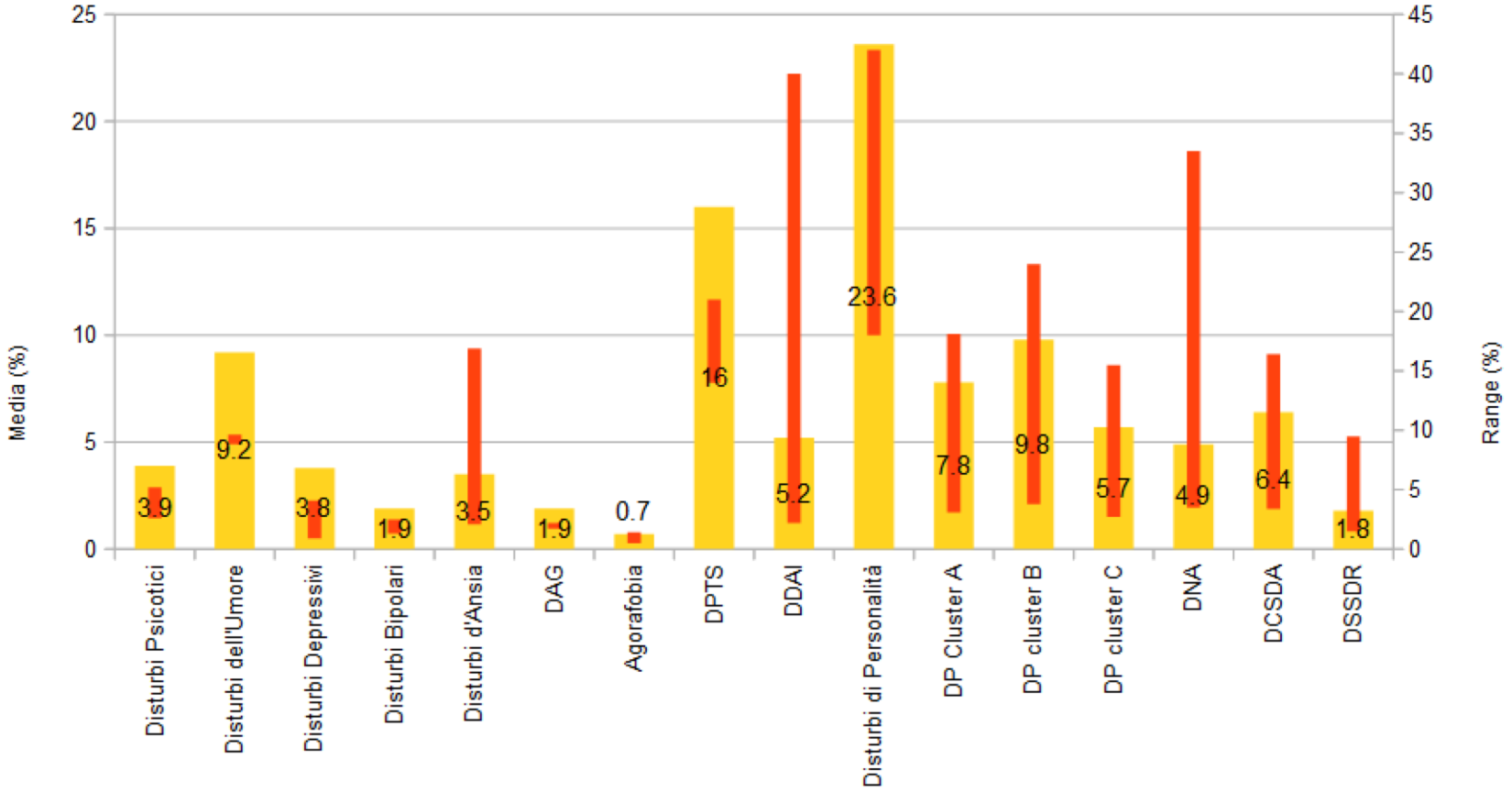
Prevalenza di DP (q.t.) nelle PcDI/DSA-BF



1. Borthwick-Duffy SA. Epidemiology and prevalence of psychopathology in people with mental retardation. J Cons Clin Psy, 1994; 62: 17-27
2. Cooper SA., Smiley E., Morrison J., et al. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. British J Psy 2007; 190: 27-35.
3. Deb S., Thomas M., and Bright C. Mental disorder in adults with intellectual disability. I: prevalence of functional psychiatric illness among a community-based population aged between 16 and 64 years. J Intell Dis Res, 2001; 6: 495-505
4. Cooper, S.-A. Psychiatry of elderly compared to younger adults with intellectual disability. J of Appl Res in Intellectual Disability 1997, 10 (4): 303–311.
5. Meltzer, H., Gill, B., Petticrew, M. & Hinds, K. (1995) The prevalence of psychiatric morbidity among adults living in private households: OPCS survey of psychiatric morbidity in Great Britain, report 1. London: HMSO.
6. Borthwick-Duffy, S. A. & Eyman, R. K. (1990) Who are the dually diagnosed? American Journal of Mental Retardation 94 586–595.
7. Reiss, S. Prevalence of dual diagnosis in community-based day programs in the Chicago metropolitan area. Am J Mental Ret 1990, 94: 578–585.
8. Lund, J. The prevalence of psychiatric morbidity in mentally retarded adults. Acta Psychiatrica Scandinavica 1985, 72: 563–570.
9. Corbett, J. A. (1979) Psychiatric morbidity and mental retardation. In: F. E. James and R. P. Snaith (Eds) Psychiatric Illness and Mental Handicap pp11–25. London: Gaskell Press.

Prevalenza di DP specifici nelle PcDI/DSA-BF



Comorbidity of medicaid enrolled adults with ASD

A retrospective data analysis using 2000-2008 three state Medicaid Analytic extract Adults (22-64 years) with (n = 1772) and without autism spectrum disorders.

Adults with autism spectrum disorders had significantly higher rates of:

- psychiatric comorbidity (81%)
- epilepsy (22%)
- infections (22%)
- skin disorders (21%)
- hearing impairments (18%)

- mean annual outpatient office visits (32ASD vs 8noASD)
- prescription drug use claims (51ASD vs 24noASD)
- mean annual outpatient office visits (US$4375ASD vs US$824noASD)
- emergency room (US$15,929ASD vs US$2598noASD)
- prescription drug use (US$6067ASD vs US$3144noASD)
- total expenditures (US$13,700ASD vs US$8560noASD)

The presence of a psychiatric comorbidity among adults with ASD increased the annual total expenditures by US$4952.

Vohra R, Madhavan S, Sambamoorthi U. Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. Autism. 2016 Oct 20.

Psychiatric co-occurrence in adults assessed for ASD

Table 1. Psychiatric co-morbidity in individuals assessed for possible ASD in adulthood.

	ASD group, N (%)	Non-ASD group, N (%)	χ^2 (d.f.), p**	UK Adult Psychiatric Morbidity Survey 2007[11]	ASD Group and UK Survey[11] χ^2 (d.f. = 1), p**	Non-ASD group and UK Survey χ^2 (d.f. = 1), p**
ADHD	46 (9.7)	39 (10.1)	ns	2.3%	ns	Ns
Specific phobia	2 (0.4)	2 (0.5)	ns	All phobias: 1.4%	581.68 ***	333.26***
Agoraphobia	19 (4)	7 (1.8)	ns			
Social phobia	59 (12.4)	47 (12.2)	ns			
Panic disorder	1	0	ns	1.1%	ns	
Generalised anxiety disorder	56 (11.8)	46 (11.9)	ns	4.4%	52.04***	45.08***
OCD	85 (17.9)	51 (13.2)	*3.50(1)	1.1%	603.77***	330.21***
Any anxiety disorder	186 (39.2)	127 (32.9)	*3.58(1)			
PTSD/acute stress reaction	2	0	ns	3%	10.73***	
Depressive episode	75 (15.8)	49 (12.7	ns	2.3%	259.44***	141.17***
BPAD	4 (0.8)	5 (1.2)	5.760 (2)			
Any mood disorder	95 (20)	86 (22.3)	ns			
Specific personality disorder	4 (0.8)	8 (2.0)	ns	0.7% (antisocial, borderline personality disorders)	ns	8.82**
Psychotic disorder	10 (2.1)	16 (4.1)	ns	0.4%	24.12***	82.22***
Schizophrenia	6 (1.2)	9 (3.2)	ns			
Schizotypal disorder	4 (0.8)	7 (1.8)	ns			
Alcohol dependence	3 (0.6)	10 (2.5)	5.686 (2)	5.9%	23.44***	7.37**
Drug dependence	1	5 (1.2)	ns	3.4%	14.61***	5.07*
Eating disorder	1	0	ns	1.6%	5.72*	
Tic disorder	7 (1.4)	1	ns			
Genetic condition	6 (1.2)	6 (1.5)	ns			

ASD: autism spectrum disorder; d.f.: degree of freedom; ADHD: attention deficit hyperactivity disorder; ns: not significant; OCD: obsessive compulsive disorder; PTSD: post-traumatic stress disorder; BPAD: bi-polar affective disorder.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Russell AJ, Murphy CM, Wilson E, Gillan N, Brown C, Robertson DM, Craig MC, Deeley Q, Zinkstok J, Johnston K, McAlonan GM, Spain D, Murphy DG. The mental health of individuals referred for assessment of autism spectrum disorder in adulthood: A clinic report. Autism. 2016 Jul;20(5):623-7.

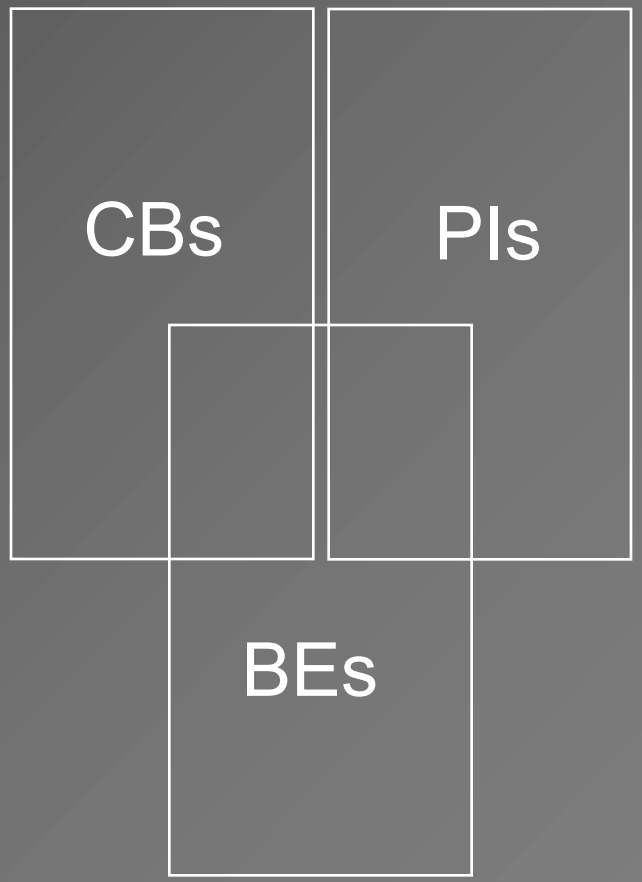
Prevalence rate (%) of PD in ID with and without ASD

	with ASD	without ASD
Depression	49	10
Mania	47	8
Eating Disorders	58	21
Schizophrenia	16	7
Anxiety	42	25

Bradley E.A. and Bolton P. Episodic psychiatric disorders in teenagers with learning disabilities with and without autism. British Journal of Psychiatry, 2006, 189: 361-366
Bradley E.A., Summers J.A., Wood H.L., Bryson S.E. Comparing rates of psychiatric and behavior disorders in adolescents and young adults with severe intellectual disability with and without autism. J of Autism and Developmental Disorders, 2004; 34(2): 151-161
Cervantes PE, Matson JL. Comorbid Symptomology in Adults with Autism Spectrum Disorder and Intellectual Disability. J Autism Dev Disord. 2015 Dec;45(12):3961-70.

INTERPRETATION OF BEHAVIOURAL EPIPHENOMENA

- Lack of Skill
- Lack of Self Regulation
- Lack of Discrimination
- Lack of Motivation
- Sensory aspects
- Coping with distractions
- Familiarity of environment
- Predictability
- Schema - rules, expectations
- Choice and level of control
- Quality of activities
- Attitudes
- Beliefs
- Values
- Physical pain
- Psychological distress
- Mental malfunction



Linda Baudewijns, Els Ronsse, Valerie Verstraete, Bernard Sabbe, Manuel Morrens, Marco O. Bertelli. Problem Behaviours And Major Depressive Disorder In Adults with Intellectual Disability and Autism. Psychiatry Research, 2018; 270: 769-774

PROBLEM BEHAVIOURS IN IDD

H—Assess for possible physical health problems, (consult the above physical health recommendations for head-to-toe sequence of common medical concerns), pain, and adverse and other side effects of medications

E—Facilitate “enabling environments” that meet these unique developmental needs and can diminish or eliminate BTC. Work with an interprofessional team and caregivers to address problematic environmental circumstances (see guidelines 1, 2, 26).73 Ascertain whether existing supports match needs (see guideline 8).258 Plan for a functional behavioural assessment by a behavioural therapist or psychologist

L—Screen for distressing Life experiences that might be contributing to BTC

P—Having attended to the above, consider psychiatric conditions (eg, adjustment difficulties, mood and anxiety concerns). Refer as needed for assessment to an interprofessional mental health team

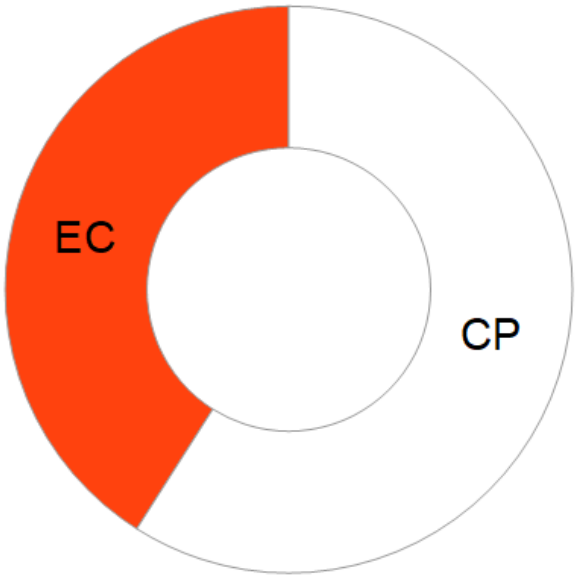
Sullivan WF et al. Primary care of adults with intellectual and developmental disabilities. 2018 Canadian consensus guidelines. Canadian Family Physician April 2018, 64 (4) 254-279;

BEHAVIOURAL EQUIVALENTS

- Determining whether PBs are the result of organic conditions, co-occurrent PD, environmental influences, or a combination of these, is always very difficult and the same behaviour can be interpreted very differently by the different professionals, even within the same staff, with relevant implications for intervention.
- Some studies demonstrated a relationship between PBs and PD[1], particularly strong in individuals with lower level of functioning[2], and **some behavioural equivalents have been identified for specific symptoms**[3].
- Charlot suggests the course of the behaviour in respect to other possible symptoms of a PD as a main reference to decide whether the behaviour can be considered a symptom equivalent[4].
- Other studies found **no evidence** that PBs were behavioural equivalents of PD[5].
- Some authors sustain that PBs and maladaptive behaviours should be interpreted as **nonspecific indicators of emotional distress** rather than atypical symptoms[6].

1. Emerson et al., 1999; Felce et al., 2009; Hemmings et al., 2006; Kishore et al., 2005; Moss et al., 2000; Rojahn et al., 2004. 2. Felce et al., 2009. 3. Hurley, 2006. 4. Charlot, 2005. 5. Tsiouris et al., 2003. 6. Rojahn and Meier, 2009

CAUSE DI COMPORTAMENTO PROBLEMA



dolore fisico

vantaggi secondari

fenotipi comportamentali

fattori ambientali

altri sintomi o altri EC

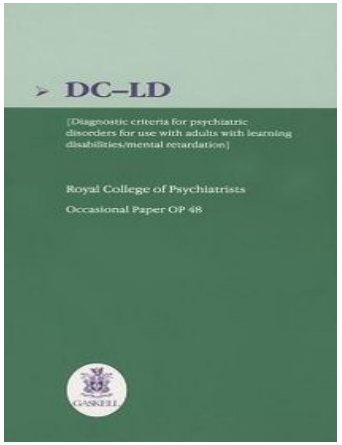
problemi organici

fattori psicologici

fattori socio-relazionali

MANUALI DIAGNOSTICI PER I DSI/DSA

Diagnostic Criteria for Learning Disability (DC-LD; 2001) adattamento dell'ICD-10 del Royal College of Psychiatrists (UK)



Diagnostic Manual – Intellectual Disability (DM-ID; 2016) adattamento del DSM-5 da parte della National Association for Dual Diagnosis (USA)

DDM: CRITERI DIAGNOSTICI PER LA DI/DSA-BF

	Criteri per la popolazione generale	Adattamento alla DI-MG e al DSA-BF
A1	Umore depresso	L'espressione del volto esprime tristezza, la mimica e la gestualità sono ridotte, oppure è presente tendenza a non sorridere o a piangere, oppure comparsa o incremento significativo di aggressività, sia fisica che verbale, verso altre persone o oggetti, oppure comportamenti auto-lesivi o auto-mutilanti
A2	Perdita d'interesse e piacere	Incapacità di divertirsi con le attività o gli oggetti prima apprezzati, divertenti o interessanti, oppure riduzione della partecipazione a queste stesse attività, oppure ritiro sociale (riduzione nell'iniziativa all'interazione sociale o aumentata tendenza al ritiro negli approcci d'interazione fatti da altri), oppure riduzione della cura di sé (incluso il rifiuto di cooperare nella cura fisica abituale fornita da altri), oppure riduzione nella quantità di eloquio, fonazione o altra forma di comunicazione/espressione
A3	Umore irritabile	Riduzione del livello di tolleranza, espressa con comportamenti oppositivi, fughe o con aggressività fisica o verbale, in risposta a stimoli minori generalmente ben tollerati;
A4	Diminuita energia o aumentata affaticabilità	Riduzione significativa della quantità di attività o della durata delle attività principali, inclusa la cura di sé (es. difficoltà a mantenere la cooperazione nella cura fisica abituale fornita da altri), oppure comparsa di agitazione quando invitato a svolgere attività che richiedano uno sforzo fisico, oppure allungamento del tempo trascorso a sedere o a letto, oppure riduzione nella quantità di eloquio, fonazione o altra forma di comunicazione/espressione
A5	Perdita di sicurezza o di autostima	Perdita o riduzione significativa della disponibilità a intraprendere nuove attività, oppure incremento della ricerca di supporto, oppure allungamento dei tempi di latenza prima dell'esecuzione di compiti e attività noti, oppure comparsa o intensificazione di condotte di evitamento

PSYCHOPATOLOGY SCREENING TOOLS IN DID

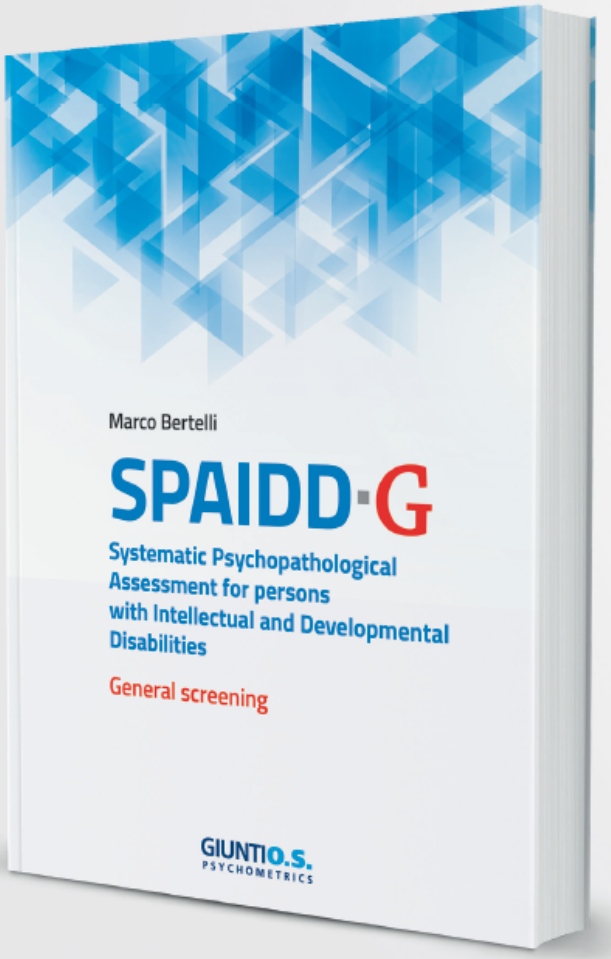
PIMRA
Psychopathology Instrument for Mentally Retarded Adults

DASH
Diagnostic Assessment for the Severely Handicapped

PASS-ADD
Psychiatric Assessment Schedule for Adults with Developmental Disabilities Checklist

VAP-H
Valutazione degli Aspetti Psicopatologici nell'Handicap

SPAIDD
(Systematic Psychopathological Assessment for people with Intellectual and Developmental Disabilites)



Marco Bertelli

SPAIDD·G

Systematic Psychopathological Assessment for persons with Intellectual and Developmental Disabilities

General screening

GIUNTI O.S.
PSYCHOMETRICS

PROGETTO SPAIDD
(SYSTEMATIC PSYCHOPATHOLOGICAL ASSESSMENT for persons with INTELLECTUAL AND DEVELOPMENTAL DISABILITIES)

Valutazione psichiatrica basata sull' osservazione comportamentale

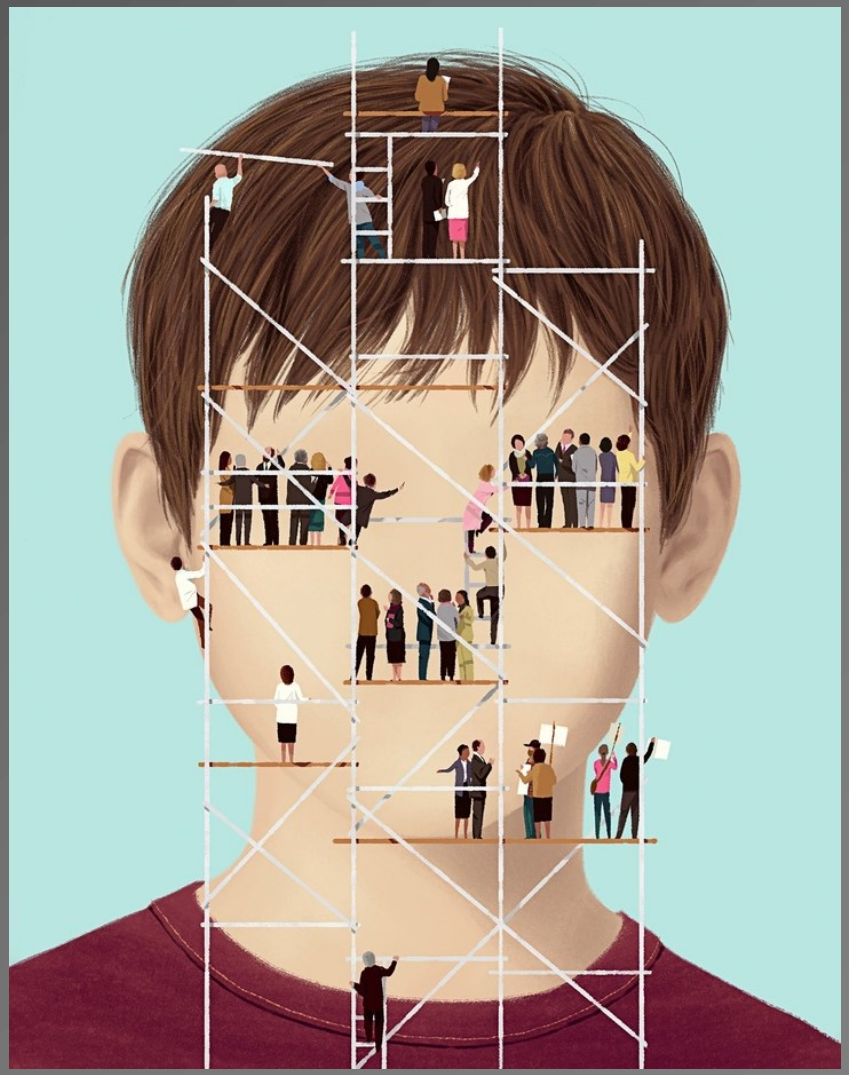
Fornire strumenti diagnostici validi e di facile impiego alle professionalità operanti nei DSI
Stime epidemiologiche dei disturbi psichiatrici nel DSI

- SPAIDD-G (orientamento diagnostico Generale)
- Creazione di strumenti SPAIDD, specifici per singoli ambiti diagnostici che, includendo criteri cronologici, permettano di fornire diagnosi precise:
  - SPAIDD-ASD, per i Disturbi Pervasivi dello Sviluppo
  - SPAIDD-P, per i disturbi Psicotici
  - SPAIDD-A, per i disturbi d' Ansia (escluso il DOC)
- **SPAIDD-M,** per i disturbi dell' Umore
  - Consente di formulare diagnosi specifiche (Depressione Maggiore, Disturbo Bipolare I, Disturbo Bipolare II, Distimia, Ciclotimia, Disturbo Disforico Premestruale) secondo i criteri del DSM-5

Bertelli M, Scuticchio D, Ferrandi A, Lassi S, Mango F, Ciavatta C, Porcelli C, Bianco A, Monchieri S. Reliability and validity of the SPAID-G checklist for detecting psychiatric disorders in adults with intellectual disability. Res Dev Disabil. 2012 Mar-Apr;33(2):382-90.

PROBLEMATICHE EMERGENTI

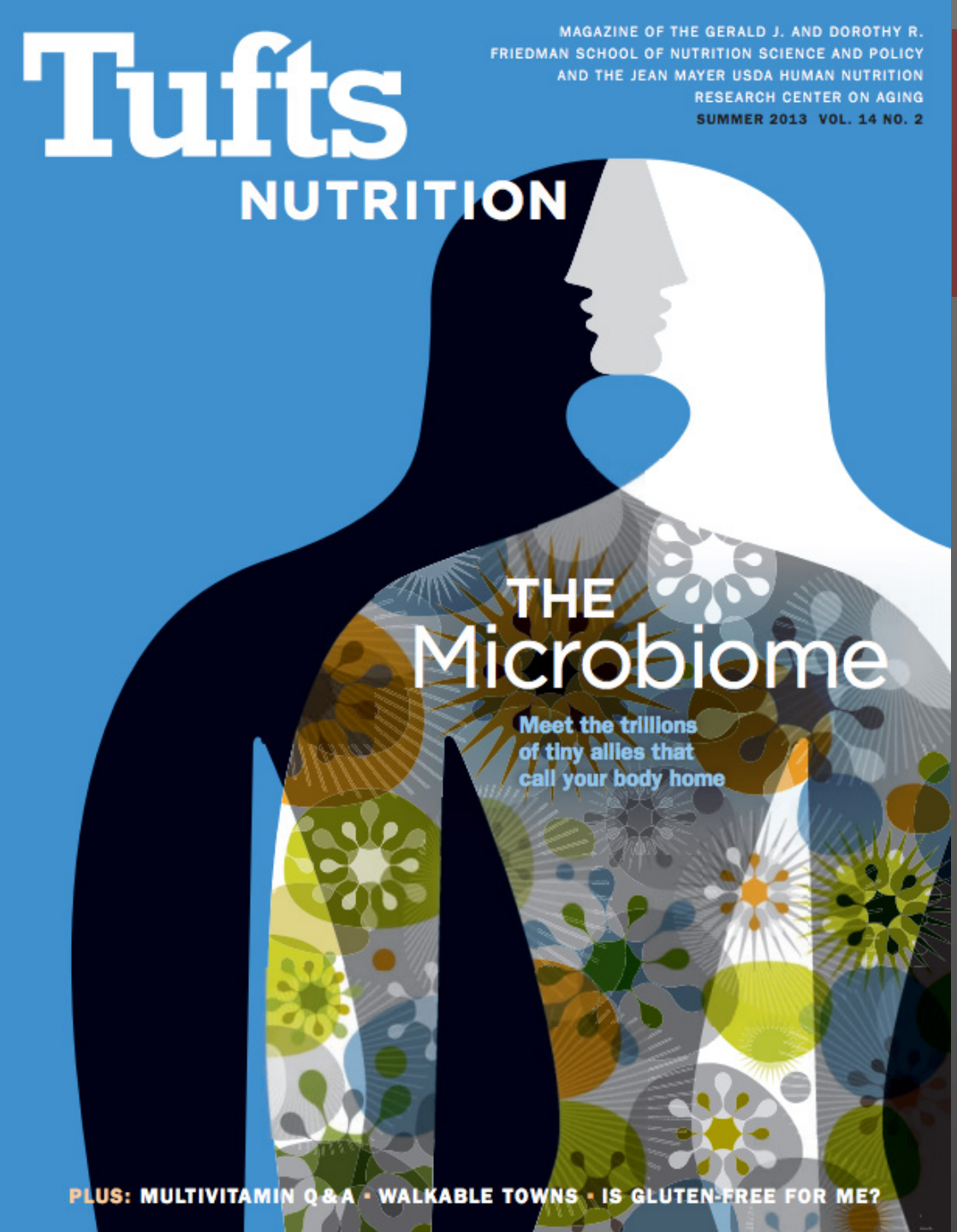
- Ampio uso
  - quantità e durata
- mancanza di ricerca
- indicazioni
- difficoltà diagnostiche e fenomenica dei disturbi psichiatrici
- uso off-label
- sicurezza e tollerabilità
- misure di esito
- uso interdisciplinare
- aspetti etici



RIFERIMENTI CONCETTUALI
PER GLI INTERVENTI PSICOFARMACOLOGICI NEI DSA

- vulnerabilità multi-sistemica sequenziale
- multi-disciplinarietà
- trasversalità nosologica
- considerazione dell'intero arco della vita
- Neuro-caratterizzazione
- pianificazione degli interventi e valutazione degli esiti centrata-sulla-persona (differenziazione delle opportunità e integrazione dei servizi)

Bertelli M.O. Giornale Italiano dei Disturbi del Neurosviluppo, in press



NEW TRENDS IN IN PSYCHIATRY OF NDD

- neuroinflammation
- oxidation
- plasticity
- gut-brain axis

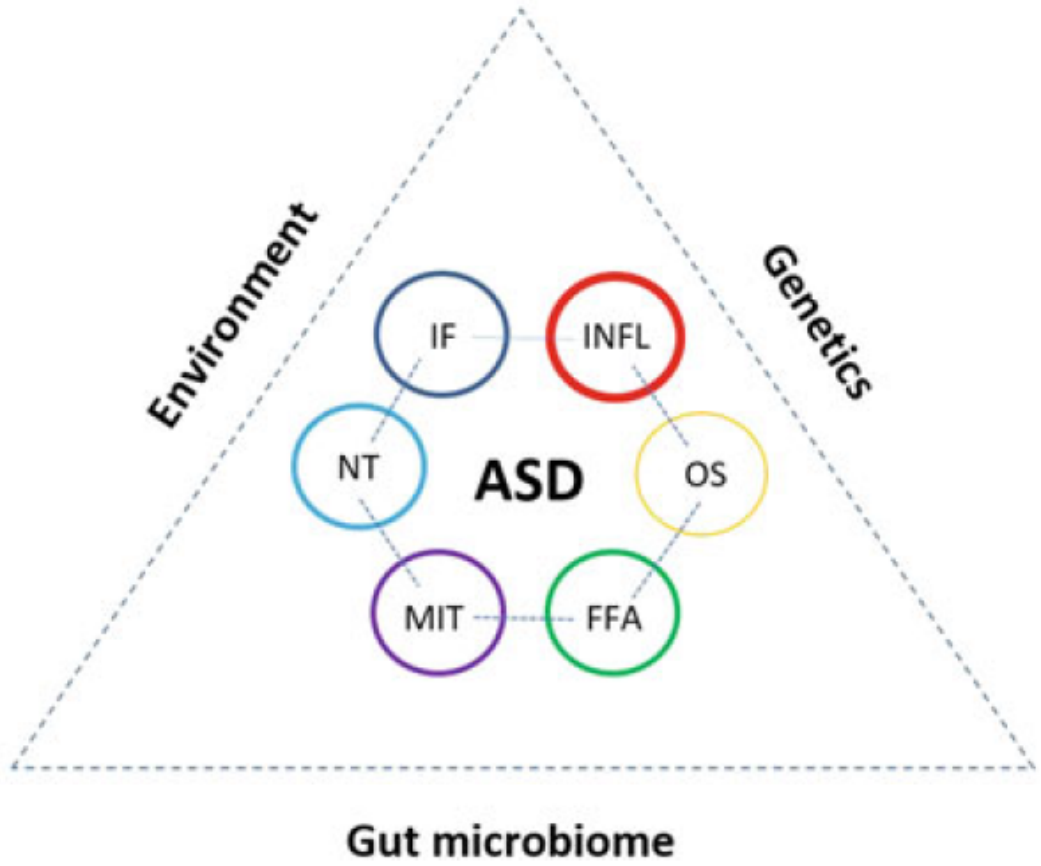


Fig. 1 Hypothetical integrative model of ASD—interactions between environment, genetics, gut microbiome and underlying biological pathways. *IF* immune function, *INFL* inflammation, *OS* oxidative stress, *FFA* free fatty acid metabolism, *MIT* mitochondrial function, *NT* neurotransmitter balance

Prata J, Machado AS, von Doellinger O, Almeida MI, Barbosa MA, Coelho R, Santos SG. The Contribution of Inflammation to Autism Spectrum Disorders: Recent Clinical Evidence. Methods Mol Biol. 2019;2011:493-510.

WPA-SPID
LINEE-GUIDA PER LA GESTIONE PSICOFARMACOLOGICA DEI COMPORTAMENTI PROBLEMA NELLE PERSONE CON DI E DSA-BF

WPA SECTION REPORT

International guide to prescribing psychotropic medication for the management of problem behaviours in adults with intellectual disabilities

SHOUMITRO DEB[1,2], HENRY KWOK[1,3], MARCO BERTELLI[1,4], LUIS SALVADOR-CARULLA[1,5], ELSPETH BRADLEY[1,6], JENNIFER TORR[1,7], JARRET BARNHILL[1,8], FOR THE GUIDELINE DEVELOPMENT GROUP OF THE WPA SECTION ON PSYCHIATRY OF INTELLECTUAL DISABILITY

[1]WPA Section on Psychiatry of Intellectual Disability; [2]Department of Psychiatry, University of Birmingham, 25 Vincent Drive, Birmingham B15 2FG, UK; [3]Kwai Chung Hospital, Hong Kong, China; [4]Italian Society for the Study of Mental Retardation, Florence, Italy; [5]University of Cadiz, Spain; [6]Department of Psychiatry, University of Toronto, Canada; [7]Monash University, Melbourne, Australia; [8]University of North Carolina School of Medicine, Chapel Hill, NC, USA

World Psychiatry, 2009; 8:181-186

1. QUANDO CONSIDERARE UN FARMACO

- se non vengono identificati disturbi medici o psichiatrici devono essere presi in considerazione solo gestioni non-farmacologiche
- talora, dopo valutazione individualizzata può essere utile aggiungere una terapia farmacologica (su sintomi o su dimensioni).

  Questa strategia deve esser vista come ‘ad interim’ e si deve operare un monitoraggio attento e regolare dell’efficienza.

Bertelli M., Bianco A., Rossi M. et al. Il comportamento problema negli adulti con disabilità intellettiva: guida internazionale all'utilizzo della terapia farmacologica. Versione italiana del documento WPA-SPID. In press

CONSIDERARE L'INTERRUZIONE DEL TRATTAMENTO FARMACOLOGICO

Terapia non interrotta

Follow-up, Valutazione

Terapia interrotta

- rivedere le ragioni della prescrizione
- tipo, frequenza, gravità e durata del comportamento
- risposte precedenti all'interruzione
- circostanze individuali
- valutare alternative disponibili
- pianificare l'eventualità di ricadute

Sviluppare un **piano ricaduta**:
- attendere, osservare e monitorare il comportamento
- specificare una scala cronologica
- considerare un intervento N-F
- considerare una nuova prescrizione
- riconsiderare la precedente

l'interruzione dipende da:
- tipo (es. depot vs. orale), dose, durata, eventi avversi del trattamento
- circostanze individuali

Monitorare

comportamento non peggiorato

comportamento peggiorato

continuare con revisioni regolari

considerare un piano ricaduta

PROBLEMATICHE EMERGENTI

- Ampio uso
  - quantità e durata
- mancanza di ricerca
- indicazioni
- difficoltà diagnostiche e fenomenica dei disturbi psichiatrici
- uso off-label
- sicurezza e tollerabilità
- misure di esito
- uso interdisciplinare
- aspetti etici

CONSENSO INFORMATO

- Libero (libertà morale)
- Personale
- Specifico
- Consapevole

CONSENSO NELLA DI: SPERIMENTAZIONE

- la sottoposizione di una persona con disabilità a sperimentazione clinica senza un adeguato consenso informato individua un reato di violenza privata (articolo 610 del codice penale)

- in Italia il Dlgs 211/2003 prevede che la persona sottoposta a sperimentazione dia consenso informato attraverso dichiarazione scritta, datata e firmata, resa spontaneamente, dopo esaustiva informazione circa la natura, il significato, le conseguenze ed i rischi della sperimentazione e dopo aver ricevuto la relativa documentazione appropriata.

- tale decisione può essere espressa o da un soggetto capace di dare il consenso, ovvero dal suo rappresentante legale (art. 2 comma 1 lett. l)

CONSENSO E DI NELLA SPERIMENTAZIONE: NON SOLO UN PROBLEMA DI GIUDIZIO

- tener conto delle caratteristiche emotive
- lasciare spazio adeguato fra informazione fornita e raccolta del consenso (per la caratteristica lentezza cognitiva) per mezzo di colloqui brevi (per la scarsa tenuta dell'attenzione) e ripetuti
- considerare il rapporto fra la quantità di informazioni fornite e l'effetto sulla comprensione generale di ciò che viene richiesto: a volte informazioni troppo particolareggiate confondono il soggetto
- usare una terminologia non specialistica
- attuare una forma non standardizzata di informazione
- considerare il problema della "condiscendenza istituzionale", cioè la possibilità «di aderire per condiscendenza verso l'istituto e/o per gratitudine nei confronti del medico

"La sperimentazione clinica in soggetti disabili" (Gian Luigi Mansi, Massimo Molteni) da "Manuale di Bioetica per la sperimentazione clinica e i Comitati Etici"

J Psychopharmacol. Author manuscript; available in PMC 2018 February 08.

Published in final edited form as:
J Psychopharmacol. 2018 January ; 32(1): 3–29. doi:10.1177/0269881117741766.

Autism Spectrum Disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology

Oliver D Howes, MRCPsych, PhD,
MRC London Institute of Medical Sciences, London, UK and Institute of Psychiatry, Psychology & Neuroscience, King's College London

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Tony Charman, PhD,

Consensus recommendations of pharmacological treatment of co-occurring conditions and symptoms in children and adults with ASD

	Children	Adults
Mood disorders	Decision on treatment needs to be made on a case by case basis. Follow the British Association for Psychopharmacology (BAP) guidelines for treating depression (strength of recommendation: S)	Decision on treatment needs to be made on a case by case basis. Follow the British Association for Psychopharmacology (BAP) guidelines for treating depression (strength of recommendation: S)
Anxiety disorders	Consider a cautious trial of an SSRIs followed by risperidone if poor response. Monitor for worsening of anxiety in some children. (strength of recommendation: B)	Decision on treatment needs to be made on a case by case basis. Follow the British Association for Psychopharmacology (BAP) guidelines for treating anxiety (strength of recommendation: S)
Sleep disorders	Melatonin, if possible, in combination with a behavioural intervention. (strength of recommendation: A) Prolonged use of benzodiazepines and related GABA agonists is not recommended. (strength of recommendation: S)	Melatonin, if possible, in combination with behavioural intervention (extrapolation from findings in children) (strength of recommendation: S) Prolonged use of benzodiazepines and related GABA agonists is not recommended (strength of recommendation: S)
Irritability	Risperidone or aripiprazole but only when behavioural or educational approaches have failed. (strength of recommendation: A)	Decision on treatment needs to be made on a case by case basis. Aripiprazole or risperidone or an SSRI should only be considered cautiously and after considering alternatives (strength of recommendation: S)
ADHD	First line: methylphenidate Second line: atomoxetine, or α2A receptor agonist. Children with ASD may experience more side-effects and show less response than non-ASD patients with ADHD (strength of recommendation: A)	Decision on treatment needs to be made on a case by case basis. Follow the British Association for Psychopharmacology (BAP) guidelines for treating ADHD (strength of recommendation: S)
Tic disorders and Tourette's syndrome	Decision on treatment needs to be made on a case by case basis (strength of recommendation: S)	Decision on treatment needs to be made on a case by case basis (strength of recommendation: S)

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INTERVENTO FARMACOLOGICO NELLA DI E NEL DdSA

HIGHLIGHTS SU ANTIDEPRESSIVI E ANTIANSIA

SSRI

CLOMIPRAMINE

Many RCT, appears to improve irritability, OCD-type symptoms, but not consistent effect on hyperactivity[1]

FLUOXETINE

slight evidence (including a DBPCT[2]) of improvement of obsessive-compulsive symptoms and repetitive behaviours

FLUVOXAMINE

negative results in older trials, but more recent evidence of effectiveness in young adults (DBPCCS[3]) related to 5HT transporters polymorphism

CITALOPRAM AND ESCITALOPRAM

Improvements in anxiety, mood, and irritability

1. Remington et al., 2001; 2. Hollander et al., 2012; 3. Sugie et al., 2005

Table 1 Diagnoses that prompted the use of antidepressants in the study sample

Diagnosis	Treatment episodes,[a] *n*	Total episodes, %
Depression	147	61.3
Generalised anxiety disorder	24	9.9
Obsessive–compulsive disorder	22	9.1
Mixed anxiety and depressive disorder	11	4.6
Bipolar disorder	9	3.8
Behaviour disorder	8	3
Insomnia	4	1.7
Premenstrual tension	3	1.3
Phobias	2	0.8
Personality disorder	2	0.8
Schizoaffective disorder	2	0.8
Panic disorder	1	0.4
Post-traumatic stress disorder	1	0.4
Adjustment disorder	1	0.4
Atypical grief	1	0.4
Hypochondriasis	1	0.4
Mood swings	1	0.4
Schizophrenia	1	0.4

a. Total number of treatment episodes in the study sample $n = 241$.

= TCA = SSRI = SARI
= SNDI = SNRI

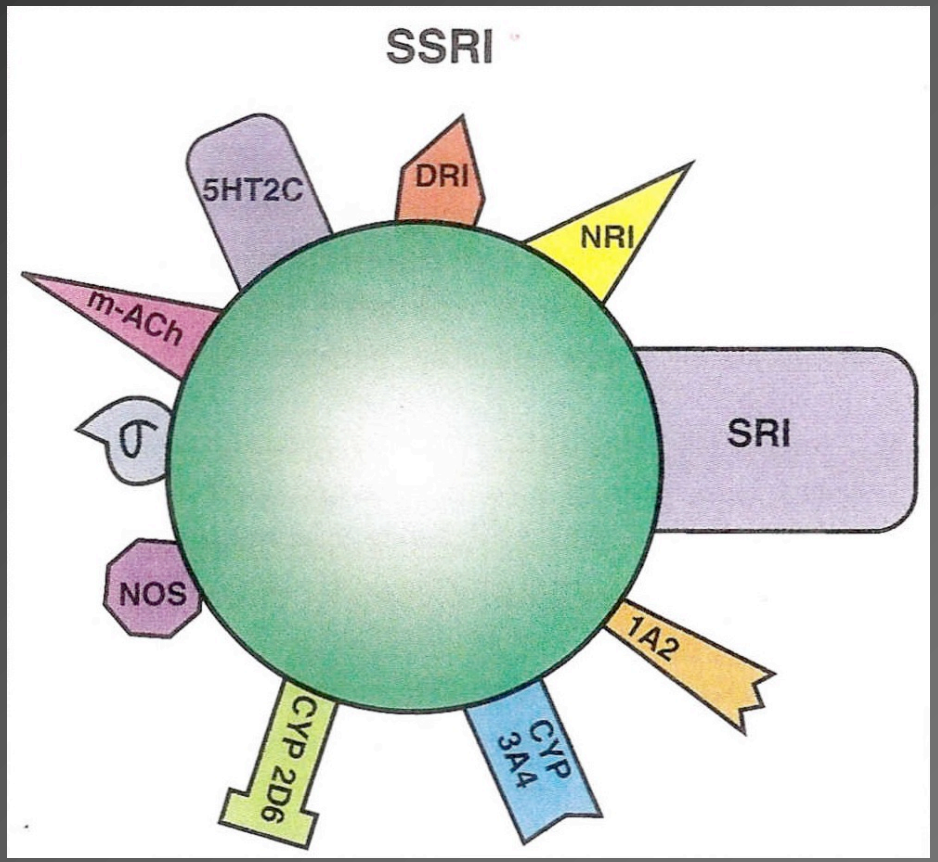
Table 2 Types of antidepressants used in the study sample and average dosage

Antidepressant	Frequency	Per cent	Average dose, mg (range)
Citalopram	104	43.2	18.7 (8–40)
Fluoxetine	43	17.8	20.6 (10–60)
Escitalopram	21	8.7	11.10 (5–20)
Mirtazapine	20	8.3	24.20 (15–45)
Trazodone	14	5.8	122.8 (50–400)
Paroxetine	9	3.7	22.5 (10–40)
Venlafaxine	8	3.3	99.2 (75–150)
Sertraline	7	2.9	52.5 (25–100)
Dothiepin	7	2.9	140.5 (25–175)
Clomipramine	2	0.8	69 (10–75)
Duloxetine	2	0.8	30 (30–30)
Fluvoxamine	1	0.4	37.5 (25–50)
Imipramine	1	0.4	25
Amitriptyline	1	0.4	30
Nortriptyline	1	0.4	10

n of case note studied = 221
mostly of mild to moderate level

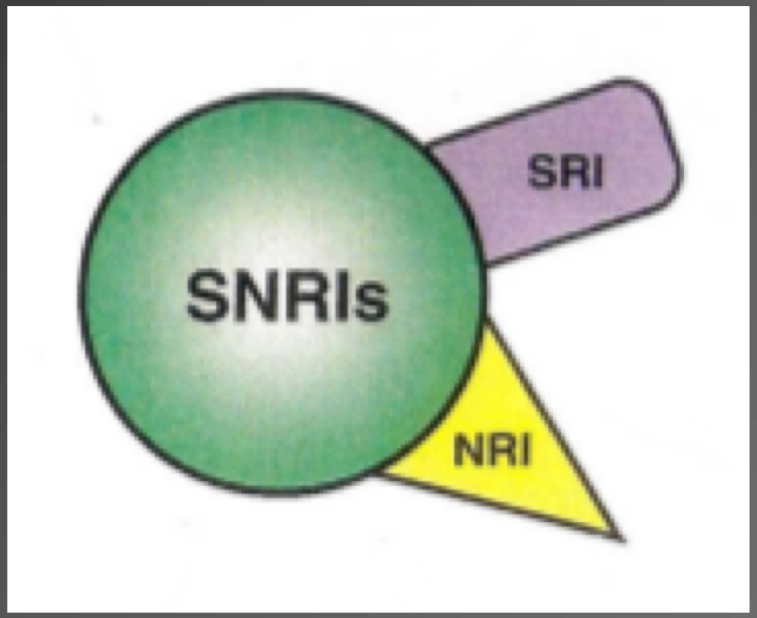
Rai et al., 2010

SSRI



	use on pwIDD	
	LIT	*PER*
Escitalopram	- -	+ + +
Citalopram	+++	-
Sertraline	+	+
Fluvoxamine	+	++
Fluoxetine	++	+
Paroxetine	+	-
others	-	-

SNRI



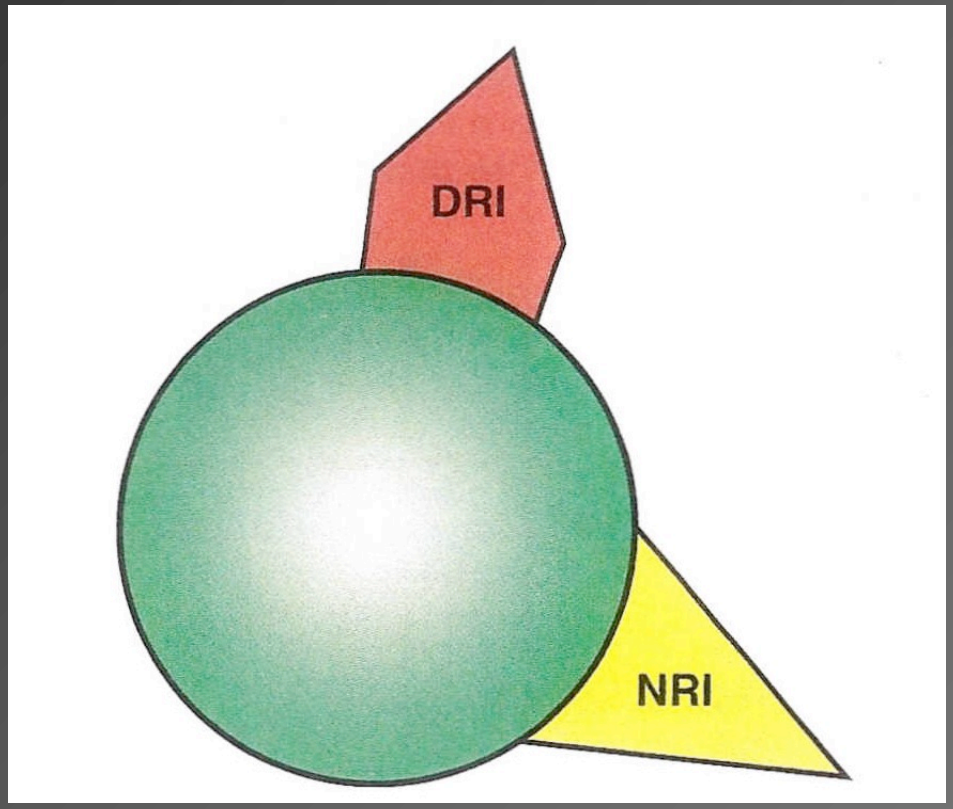
	use on pwIDD	
	LIT	*PER*
Duloxetine	- -	+ + +
Venlafaxine	-	+
Sibutramine	-	-
others	-	-

DULOXETINE: A CASE REPORT

- A young woman affected by moderate mental retardation and somatoform disorder not otherwise specified, with globus pharyngeus
- Psychometric testing of the patient was performed, in order to monitor the prescribed, duloxetine-based, treatment
- After six weeks of treatment the patient underwent full remission
- The correct identification of psychiatric comorbidity is the prerequisite for an appropriate complementary pharmacological intervention

Piacentino D, Politi R, Moscariello MM, Meuti V, Biondi M. [Mental retardation and somatoform disorder with globus pharyngeus: a case study of comorbidity]. Riv Psichiatr. 2010 Sep-Oct;45(5):334-9. Italian.

NRI and NDRI



	use on pwIDD	
	LIT	*PER*
Reboxetine	- -	+
Atomoxetine	-	+
Bupropione	-	+
others	-	-

ATOMOXETINE
AND WILLIAMS SYNDROME

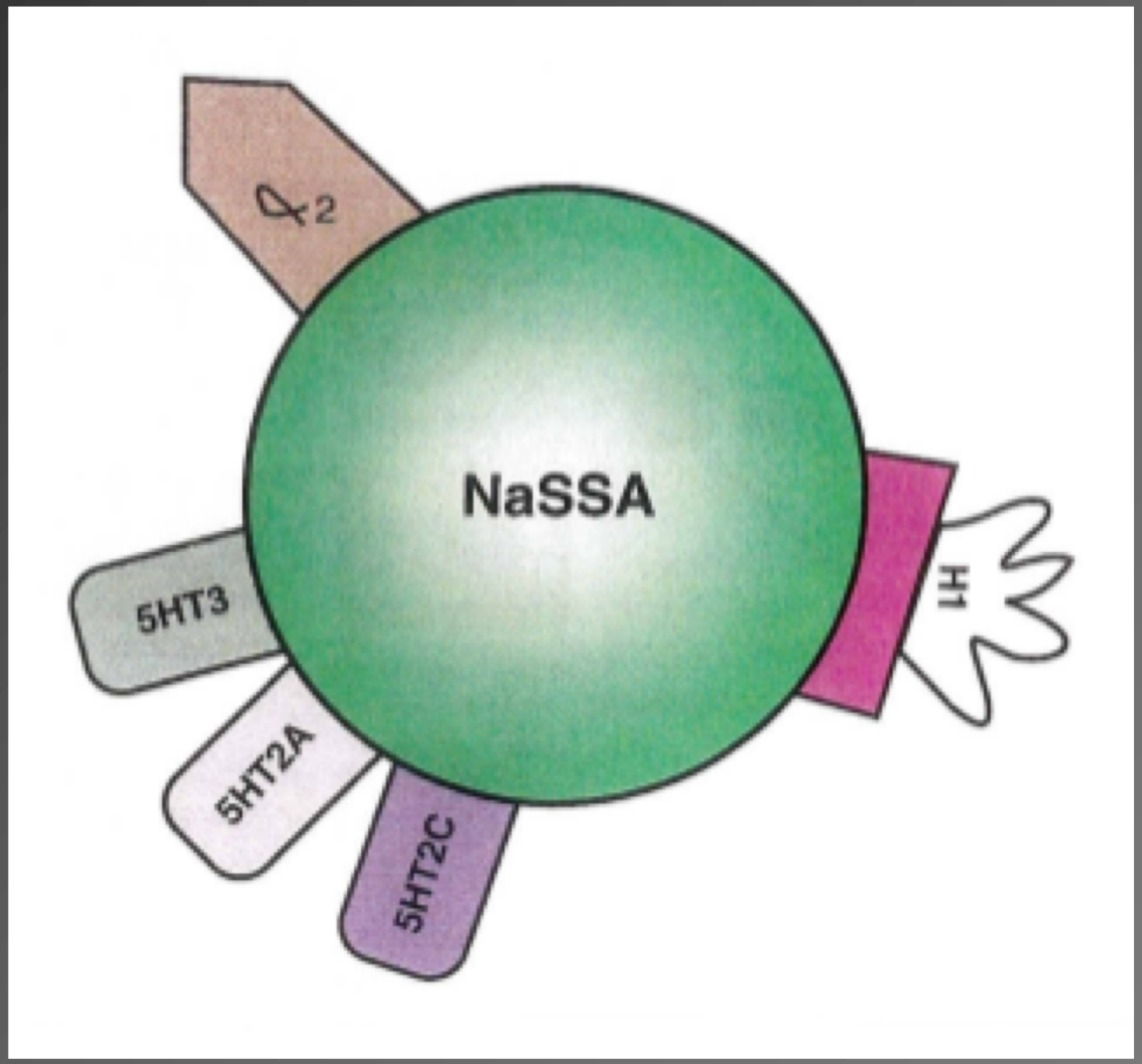
survey of 512 parents/caregivers of individuals with WS

- only 16% of individuals with WS had an age ≥18byrs
- considered to be less effective than OROS-methylphenidate (31% vs 43%)
- stomach ache was the most frequently reported side effect, followed by irritability; irritability is common also in the general population, while stomach ache is not

Martens MA, Seyfer DL, Andridge RR, Foster JE, McClure KE, Coury DL. Caregiver survey of pharmacotherapy to treat attention deficit/hyperactivity disorder in individuals with Williams syndrome. Res Dev Disabil. 2013 May;34(5):1700-9.

NaSSA/SNDI - α2 ANTAGONISTS

Serotonine and norepinephrine disinhibitors



Mirtazapine

Mianserine

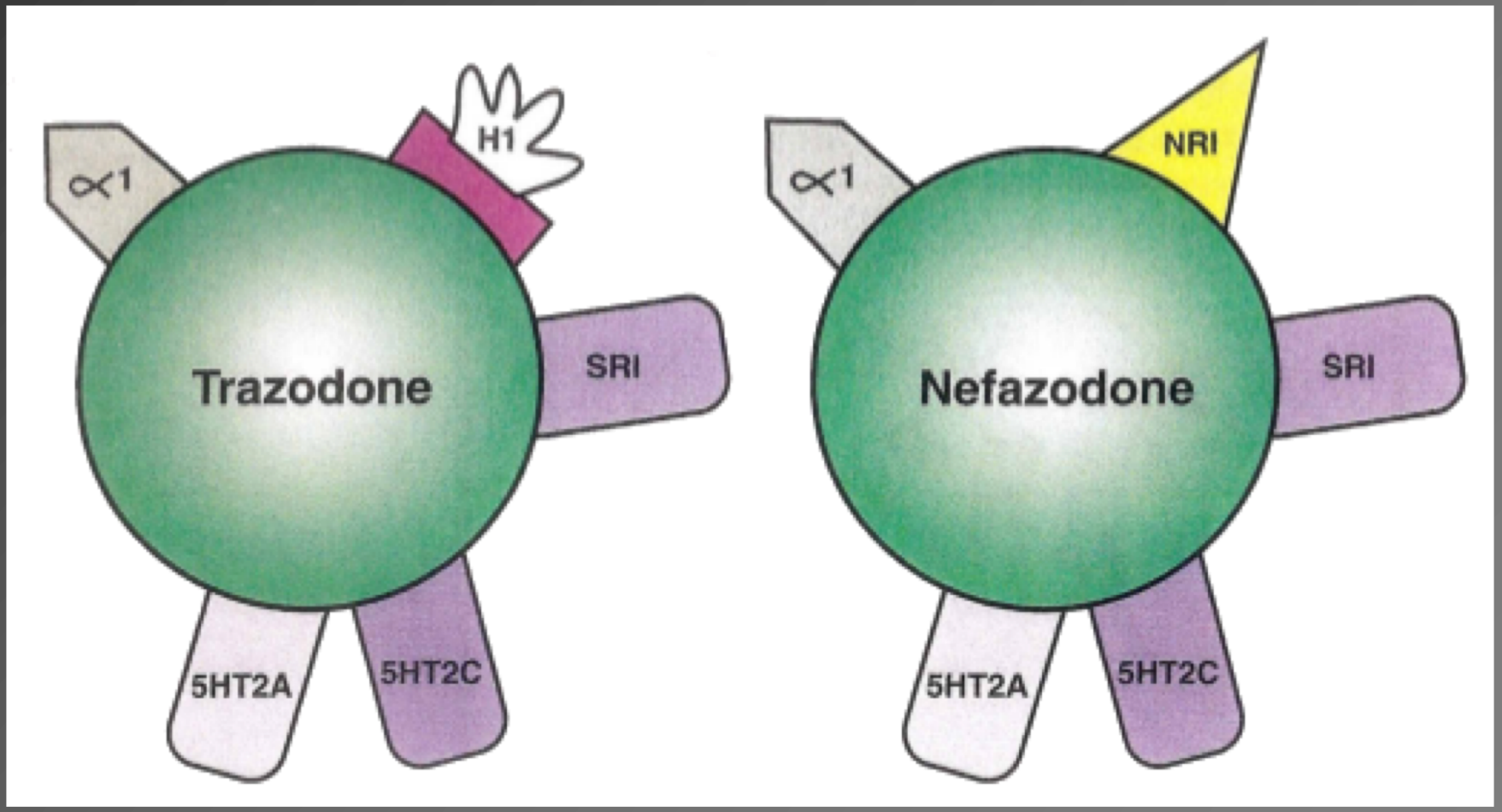
Quetiapine

Asenapine

etc

SARI

Serotonine antagonist/reuptake inhibitor



THE MELATONERGIC SYSTEM IN PB of ID

- persons with ID and sleep disorder seem to have a higher prevalence rate of problem behaviours (PB)
- treatment with exogenous melatonin seems to determine a temporal anticipation of the physiological release of endogenous hormone and qualitative and quantitative improvement of sleep (latency in falling asleep, number and length of night awakes, sleep total length), as well as PB
- response to melatonin fades out across weeks and reappears only after a considerable dose reduction
- renal clearance and saliva and plasma concentrations indicate that efficacy reduction across time is linked to metabolism increase (CYP 1A2)

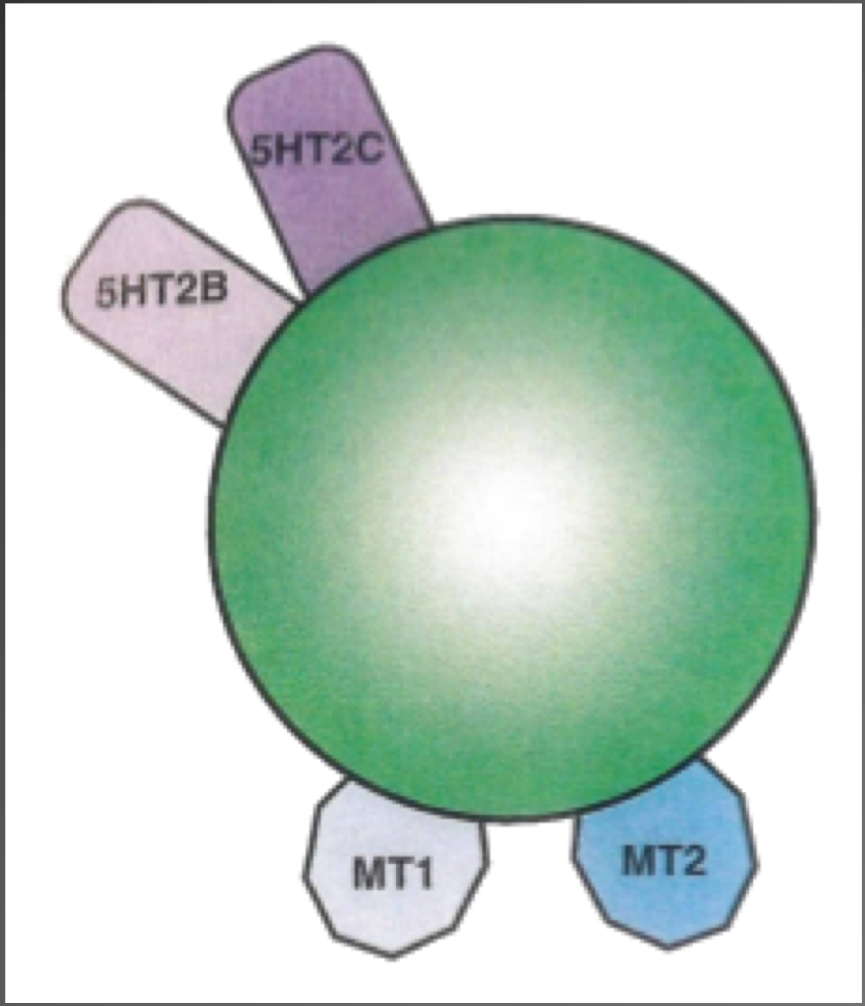
Braam W, Didden R, Maas AP, Korzilius H, Smits MG, Curfs LM. Melatonin decreases daytime challenging behaviour in persons with intellectual disability and chronic insomnia. J Intellect Disabil Res. 2010 Jan 1;54(1):52-9.
Braam W, van Geijlswijk I, Keijzer H, Smits MG, Didden R, Curfs LM. Loss of response to melatonin treatment is associated with slow melatonin metabolism. J Intellect Disabil Res. 2010 Jun;54(6):547-55.

MELATONIN

- Increasingly used to manage sleep disorders
- In the last 5 years mounting evidence (RCT, open-label, PC) of effectiveness on sleep quality and quantity
- Increased effectiveness in combination with CBT

Malow et al., 2012; Cortesi et al., 2012

AGOMELATINE



5HT 2C and 2B antagonist

MT1 and MT2 ligand

Sleep alteration?

NV dystonias?

Somatic anxiety?

AGOMELATINE AND ASD

- In animals treatment with agomelatine has significantly attenuated Pre-VPA induced reduction in social interaction, spontaneous alteration, exploratory activity intestinal motility, serotonin levels and prefrontal cortex mitochondrial complex activity
- agomelatine also attenuated Pre-VPA induced increase in locomotion, anxiety, brain oxidative stress, nitrosative stress, inflammation, calcium levels and blood brain barrier leakage
- Niederhofer (Italy) found (only 3 cases) that duloxetine and agomelatine does not exceed efficacy of other antidepressants

Niederhofer H. Efficacy of duloxetine and agomelatine does not exceed that of other antidepressants in patients with autistic disorder: preliminary results in 3 patients. Prim Care Companion CNS Disord. 2011;13(1).
Kumar H, Sharma BM, Sharma B. Benefits of agomelatine in behavioral, neurochemical and blood brain barrier alterations in prenatal valproic acid induced autism spectrum disorder. Neurochem Int. 2015 Dec;91:34-45.

PSYCHOPATHOLOGICAL DIMENSIONS IN AGOMELATINE RESPONDERS

	T1	T2	T3	T4
<0,5	-	labilità affettiva ansia somatizzata ipoergia	ansia somatizzata insonnia iniziale insonnia terminale	agitazione interna* insonnia iniziale
<0,1	-	-	irritabilità	ansia somatizzata irritabilità

One-way ANOVA post-hoc * Two-Sample Kolmogorov-Smirnov Test

<0,5	-	ansia somatizzata ipoergia	ansia somatizzata irritabilità insonnia iniziale insonnia terminale	irritabilità
<0,1	-	-		ansia somatizzata

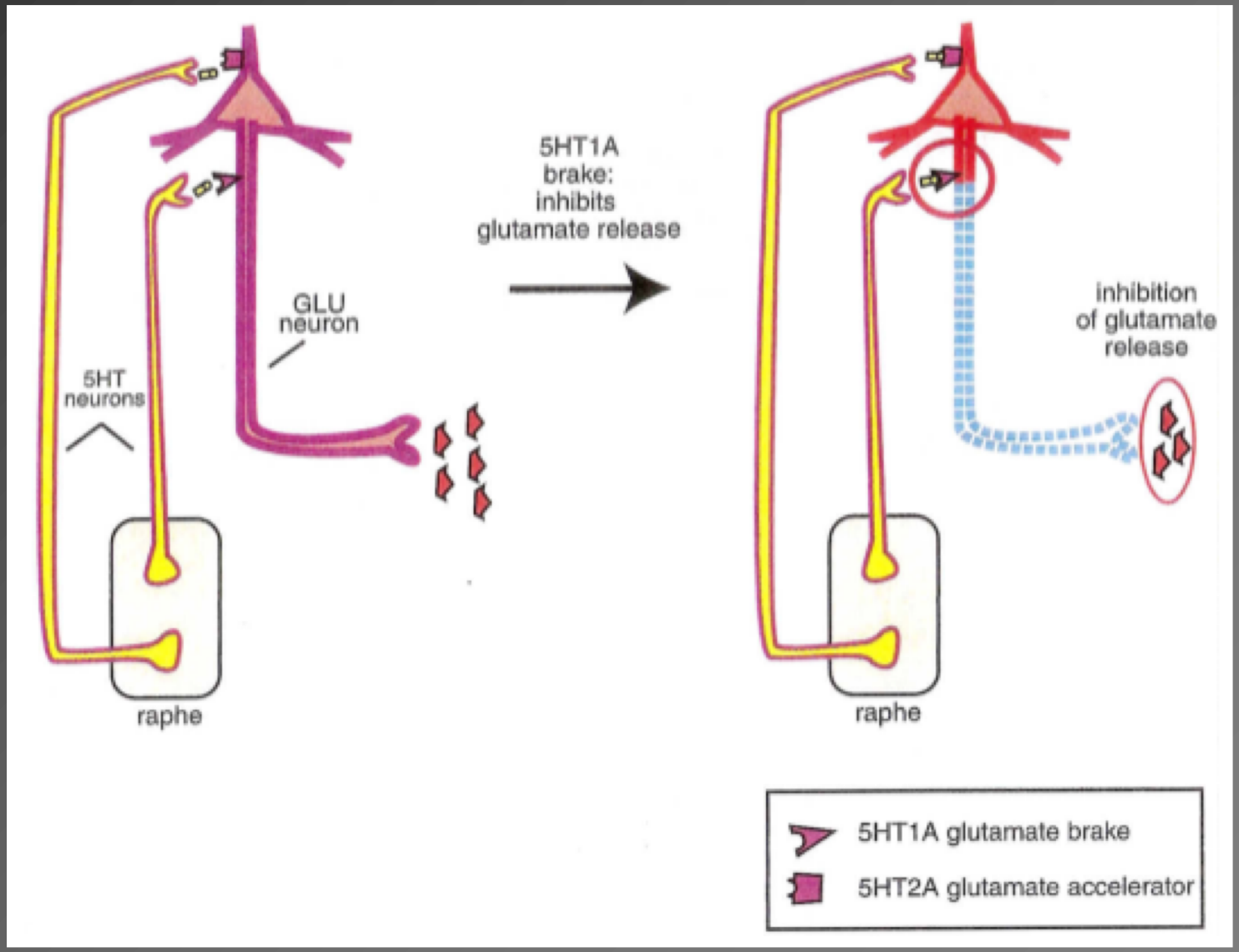
Spearrman's rho

Bertelli et al. Indicatori Di Risposta e Tailored Therapy per Un Nuovo Antidepressivo: Primi Risultati Del Progetto Rethe, 2012

AGOMELATINE RESPONDER
DIMENSIONAL PSYCHOPATHOLOGICAL PROFILE

- SOMATIC ANXIETY
- IRRITABILITY
- INITIAL INSOMNIA
- TERMINAL INSOMNIA
- HYPOERGIA
- INTERNAL AGITATION

5HT AND GLUTAMATE



GLUTAMATE RECEPTOR-RELATED

BUMETANIDE (chloride importer antagonist)

1 DBT with improvements in ASD scales, but mild hypokalemia[1]

MEMANTINE (antagonist of NMDA receptors)

Some studies (including 2 open label) – improvements in social withdrawal, inattention, irritability, hyperactivity, inappropriate speech, lethargy, and memory tests[2-4]

Main SE: sedation, rash, emesis, increased seizure frequency[2-4]

ACAMPROSATE (GABA A agonist and excitatory glutamate antagonist)

Recent open label study – improvements in social withdrawal, hyperactivity, and social responsiveness[5]

1. Lemonnier et al., 2012; 2. Erickson et al., 2007; 3. Niederhofer, 2007; 4. Owley et al., 2006; 5. Erickson et al., 2011

GLUTAMATE RRCs IN FXS

- Acamprosate and lovastatin have been beneficial in open-label trials
- The first 5 years of life may be the most efficacious time for intervention when combined with behavioral and/or educational interventions
- Minocycline, acamprosate, lovastatin, and sertraline are treatments that can be currently prescribed and have shown benefit in children with FXS

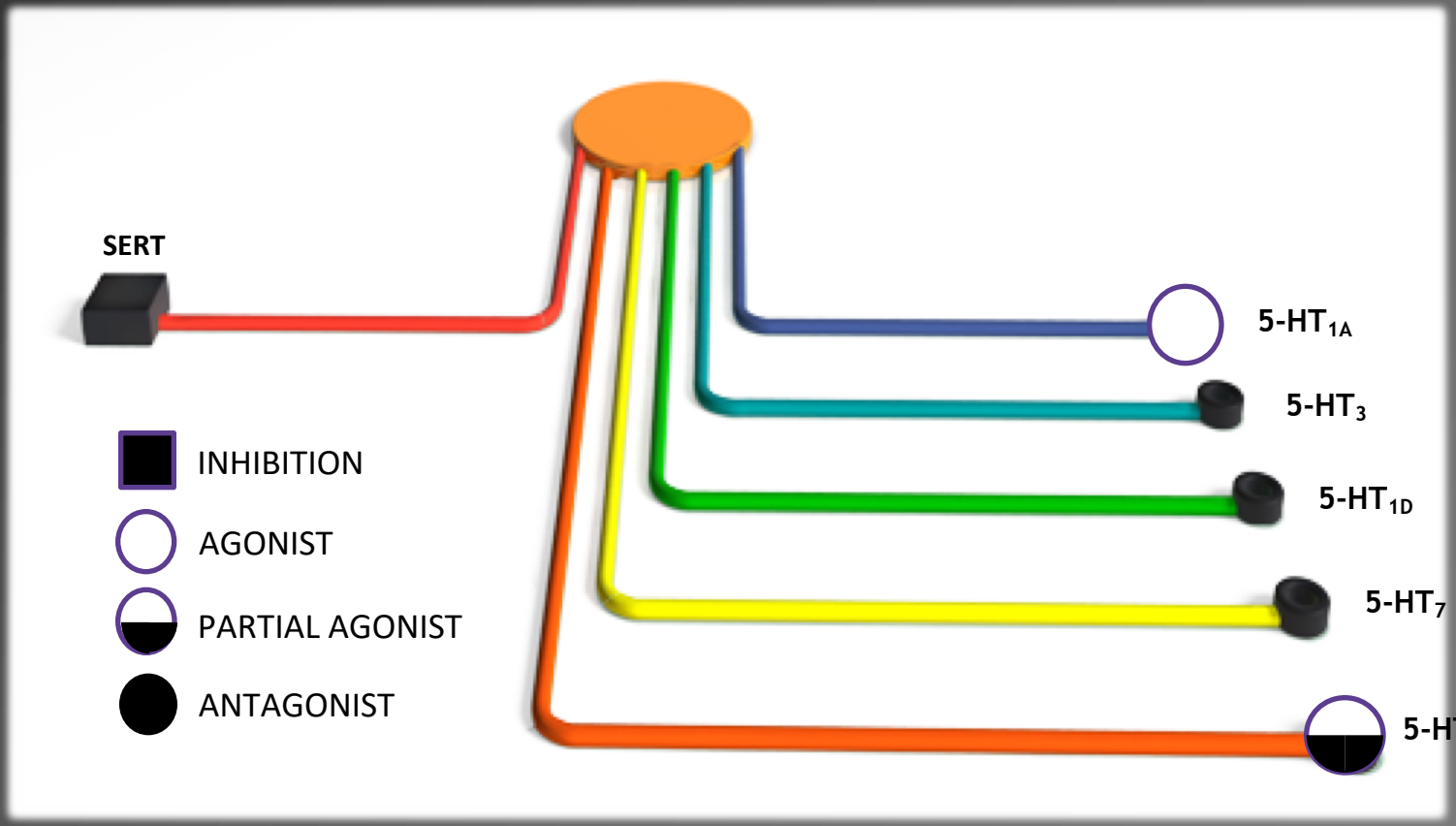
Hagerman RJ, Polussa J. Treatment of the psychiatric problems associated with fragile X syndrome. Curr Opin Psychiatry. 2015 Mar;28(2):107-12.

GABAA RECEPTOR SUBTYPES IN DOWN SYNDROME AND AUTISM

- Through the bidirectional modulation of tonic inhibition, α5-subunit-containing GABAA receptors permit the modulation of cognitive and emotional processes
- a partial inverse agonist acting at the α5-subunit-containing GABAA receptor is in a clinical trial in individuals with Down syndrome
- With regard to anxiety disorders, the viability of nonsedative anxiolytics based on the modulation of α2- and α3-subunit-containing GABAA receptors has been established in clinical proof-of-concept trials
- dysfunctional GABAergic inhibition is increasingly understood to contribute to the pathophysiology of autism spectrum disorders

Rudolph U, Möhler H. GABAA receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. Annu Rev Pharmacol Toxicol. 2014;54:483-507.

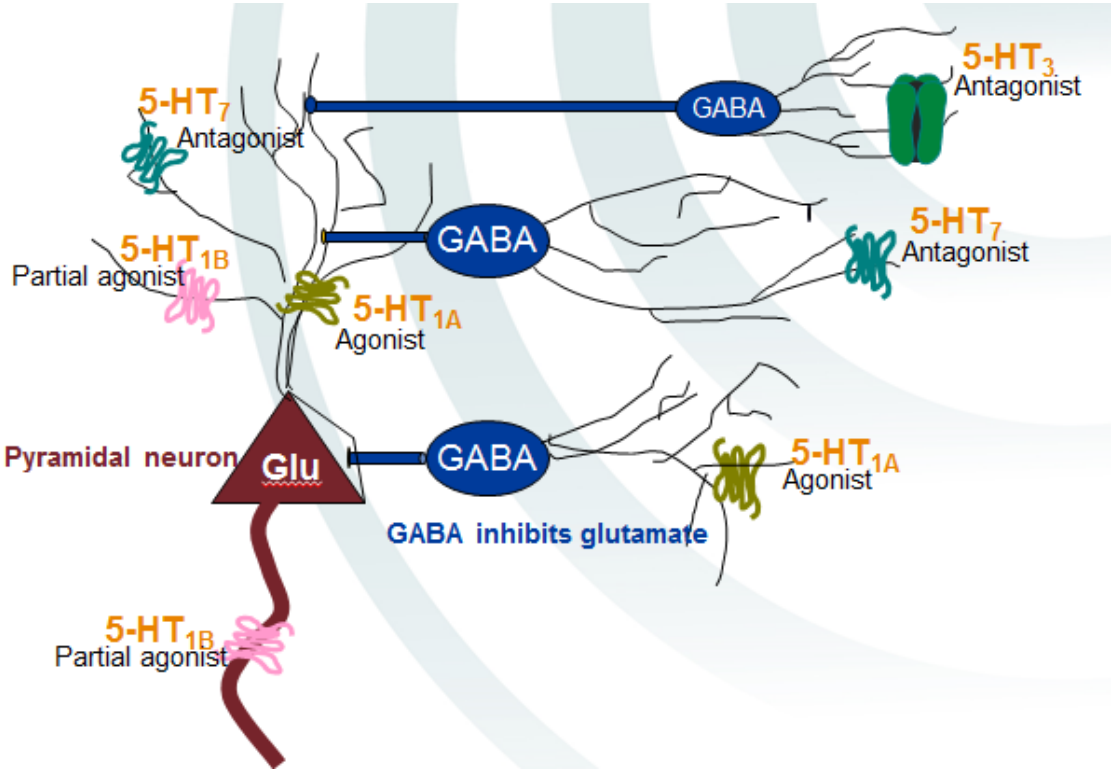
VORTIOXETINE RECEPTOR BINDING PROFILE



Vortioxetine has receptor activity and reuptake inhibition. Vortioxetine inhibits the serotonin transporter (SERT). Vortioxetine is a 5-HT1A receptor agonist, a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, and a 5-HT1B receptor partial agonist.
The clinical relevance of the pharmacologic activity is unknown.

Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): blocking 5HT3 receptors enhances release of serotonin, norepinephrine, and acetylcholine. CNS Spectr. 2015 Jun 30:1-5.

VORTIOXETINE ACTION AT 5-HT3



ANTAGONISM 5-HT3

GABA INHIBITION REMOVAL

GLUTAMATERGIC STIMULATION

REGULATION OF DOWNSTREAM RELEASE OF DA, NE, ACH, HA

Bang-Andersen et al. J Med Chem 2011;54:3206–3221; Westrich et al. Poster at IFMAD 2012; Mørk et al. Poster at ECNP 2011; Mørk et al. Poster at SOBP 2011; Pehrson et al. Poster at ECNP 2013; 6. Mørk et al. Poster at APA 2013

CORRELATIONS BETWEEN PB AND DEPRESSIVE SYMPTOMS

Two groups of persons with mild-to-moderate ID and ASD, with and without PB underwent a complex clinical (Diagnostic Manual – Intellectual Disability) and instrumental (Reiss Screen for Maladaptive Behaviour; Mini Psychiatric Assessment Schedule for Adults with Developmental Disabilities).

Instrument area scores		SGZ-aggr	SGZ-verb	SGZ-mix	SGZ total
	Symptomatological and Behavioural correlates				
RSMB-B	irritability, anxiety and sadness	-.202	-.452**	-.471**	-.468**
RSMB-P	Problems with energy, eating, sleeping and stress	-.369*	-.178	-.588***	-.566***
Mini PAS-ADD-d		-.222	-.274	-.427*	-.409*

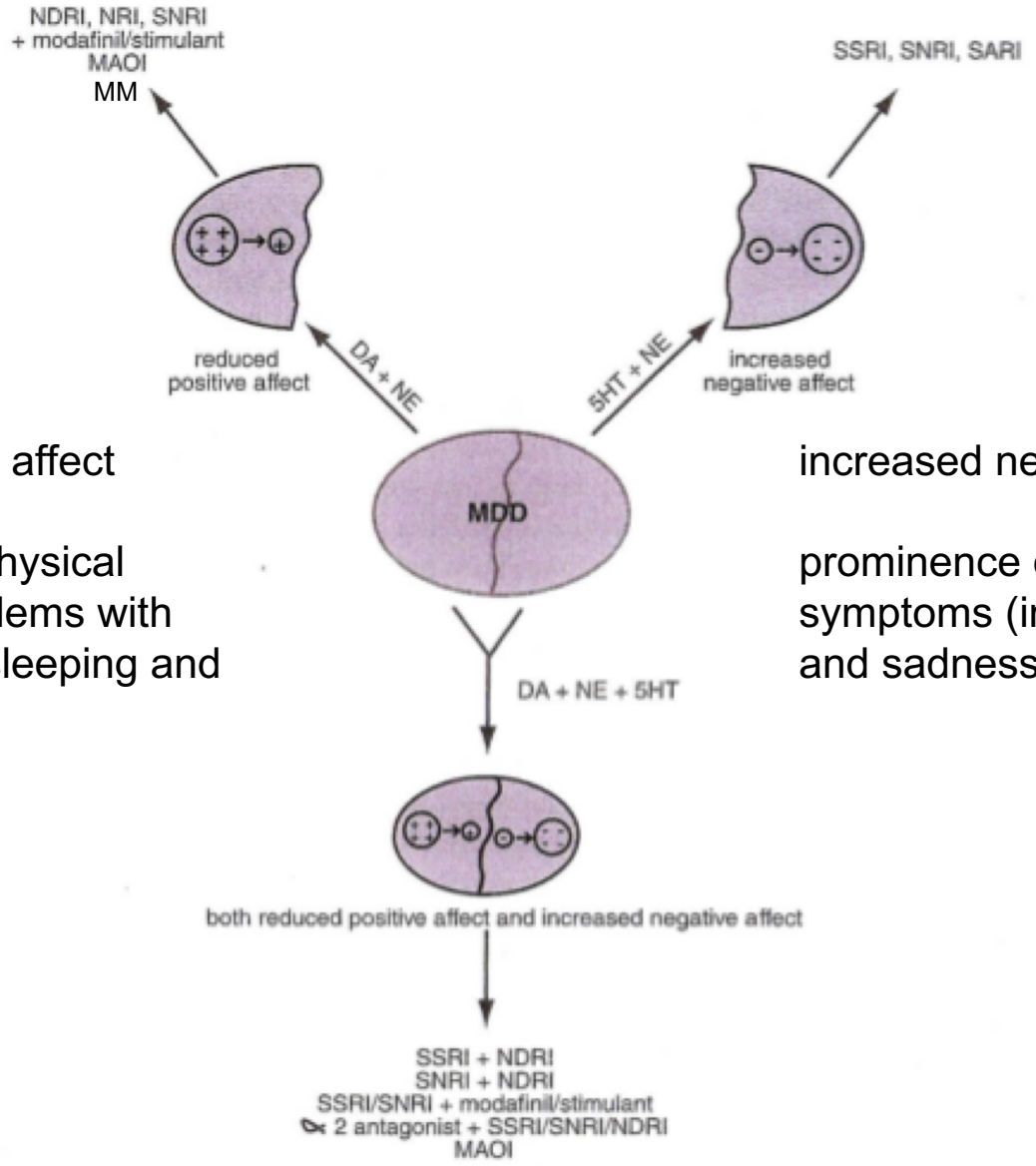
Linda Baudewijns, Els Ronsse, Valerie Verstraete, Bernard Sabbe, Manuel Morrens, Marco O. Bertelli. Problem Behaviours And Major Depressive Disorder In Adults with Intellectual Disability and Autism. Submitted to RIDD

AGGRESSIVE BEHAVIOURS AND MDD SYMPTOMS IN PERSONS WITH ID

	Syndrome and MDD symptoms specificity		
Type of aggressive behaviour	BD	MDD	
	higher association with aggressive behaviour towards other persons	lower association with aggressive behaviour towards other persons (higher association with self-injurious behavior and verbal aggression towards self)	
		prominence of emotional symptoms (irritability, anxiety and sadness)	less physical aggression
		prominence of physical symptoms (problems with energy, eating, sleeping and stress)	less verbal aggression

Linda Baudewijns, Els Ronsse, Valerie Verstraete, Bernard Sabbe, Manuel Morrens, Marco O. Bertelli. Problem Behaviours And Major Depressive Disorder In Adults with Intellectual Disability and Autism. Psychiatry Research, 2018; 270: 769-774

EVIDENCE BASED ALGORITHM FOR AD



reduced positive affect

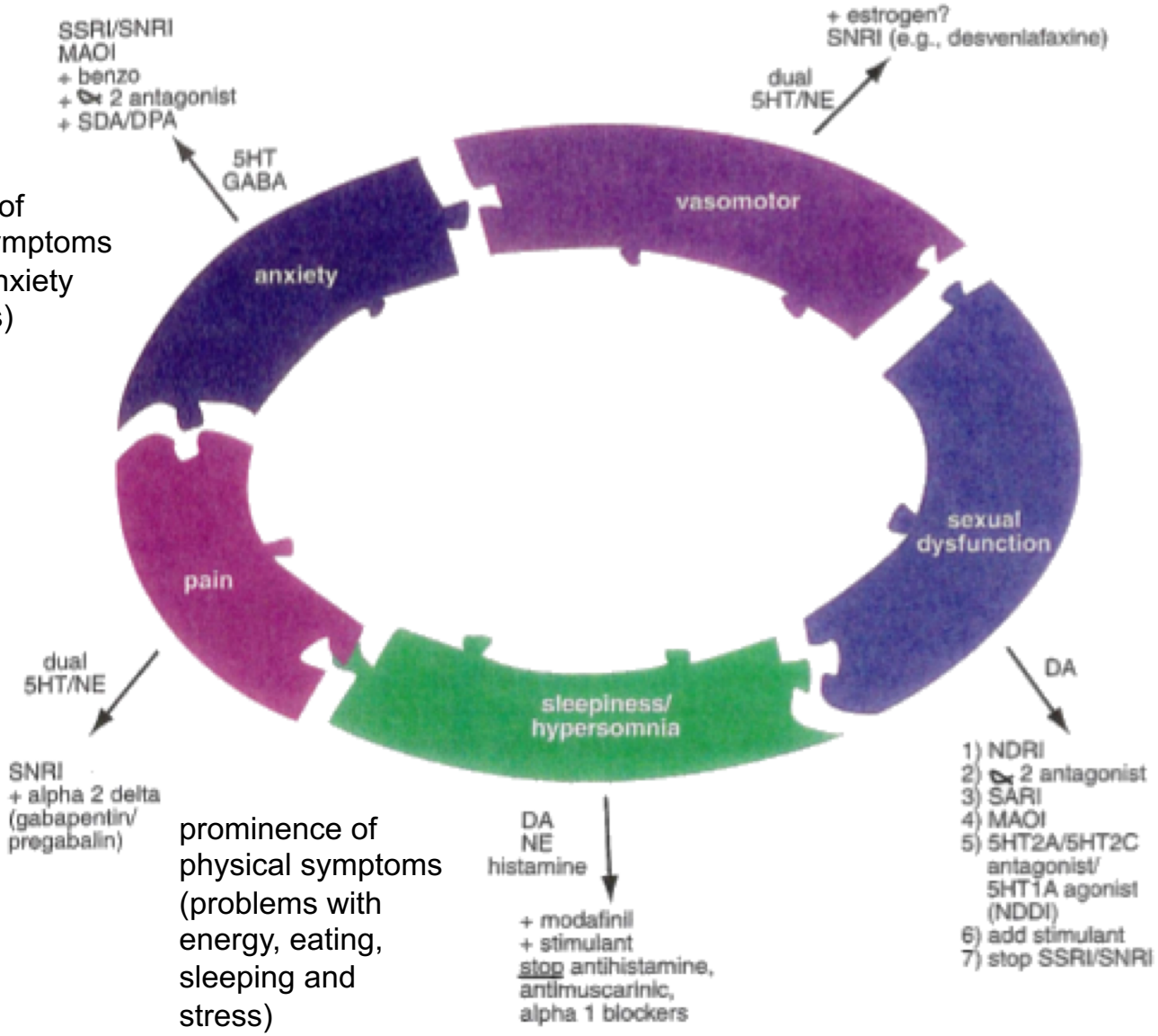
prominence of physical symptoms (problems with energy, eating, sleeping and stress)

increased negative affect

prominence of emotional symptoms (irritability, anxiety and sadness)

EVIDENCE BASED ALGORITHM FOR AD

prominence of emotional symptoms (irritability, anxiety and sadness)



prominence of physical symptoms (problems with energy, eating, sleeping and stress)

INTERVENTO FARMACOLOGICO NELLA DI E NEL DdSA

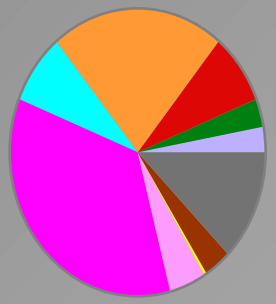
HIGHLIGHTS SU ANTIPSICOTICI

ANTIPSYCHOTICS

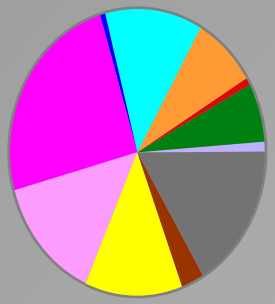
- Most studied class for efficacy and effectiveness
- Typical AP have been dropped because of low safety profile
- NGA have emerged as the first-line pharmacological treatment

ANTIPSYCHOTICS RECEPTORS BINDING PROFILE

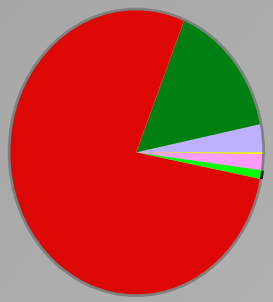
Olanzapine



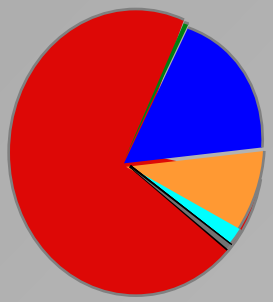
Clozapine



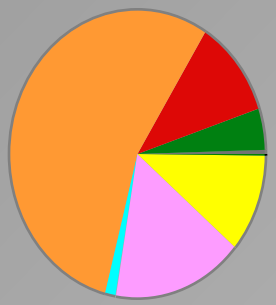
Haloperidol



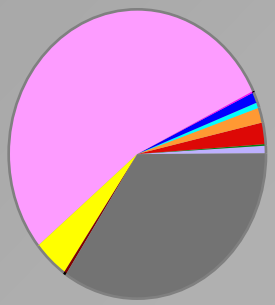
Aripiprazole



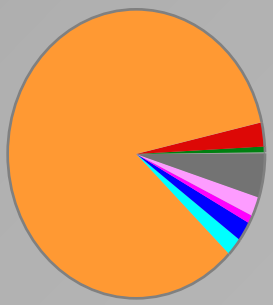
Risperidone



Quetiapine



Ziprasidone



- D_1
- D4.2
- D_2
- $5\text{-}HT_{2A}$
- $5\text{-}HT_{2C}$
- $5\text{-}HT_{1A}$
- 5-HT6
- $\alpha 1$
- $\alpha 2$
- Musc
- H1

Bymaster FP, et al. *Neuropsychopharmacology*. 1996;14(2):87-96.
Schotte A, et al. *Psychopharmacology (Berl)*. 1996;124(1-2):57-73.
Lawler CP, et al. *Neuropsychopharmacology*. 1999;20(6):612-627.
Corbett R, et al. *CNS Drug Reviews*. 1997;3(2):120-147.

TYPICAL ANTIPSYCHOTICS IN PwID/IDD

- some evidence on efficacy of TAPs in reducing aggressive behaviour in PwID
- most studied and prescribed are haloperidol, thioridazine, and chlorpromazine
- many studies pointed out low safety and low tolerability, showing a number of side effects with very high negative impact on PwID (tardive dyskinesia, neuroleptic malignant syndrome, sedation, dystonia, reduction of cognitive performance, extrapyramidal effect)
- use limited to very acute phases and at the minimum effective dose

Santosh & Baird, 1999; La Malfa & Bertelli., 2006; Deb et al., 2007; Deb & Unwin ,2007.
La Malfa & Bertelli, 2006. Advokat et al., 2000.

NGAs IN AUTISM SPECTRUM DISORDERS

RISPERIDONE is approved for the treatment of i**rritability** associated with **autistic** disorder in children and adolescents (ages **5-16 years**), including symptoms of aggression, self-injury, tantrums, and quickly changing moods. It is the first prescription medication approved by the FDA for this purpose.

ARIPIPRAZOLE is approved for the treatment of i**rritability** associated with **autistic** disorder in children and adolescents (ages **6-17 years**), including symptoms of aggression, self-injury, tantrums, and quickly changing moods.

Owen R et al. Pediatrics. 2009, Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder.

NGAs IN ID/IDD

- less effective than placebo for PBs in PwID[1]
- same effectiveness than placebo for PBs in PwID[2]
- much more effective than placebo, across the life span[3,4,5]

[1]Tyrer et al., ,2008. [2]Brylewski et al., 2007. [3]Aman et al., 2002; Snyder et al., 2002; Turgay et al., 2002.
[4] Buitelaar et al., 2001; Franco et al., 2000; McDonough et al., 2000; Zarcone et al., 2001.
[5]McAdam et al., 2002; Janowsky et al., 2003; Bokszanska et al., 2003. [6]La Malfa et al., 2006.

OLANZAPINE VS RISPERIDONE IN TREATING AGGRESSIVE BEHAVIOURS IN ADULTS WITH INTELLECTUAL DISABILITY: A SINGLE BLIND STUDY

Mario Amore[1], Marco Bertelli[2,3,5], Daniele Villani[4], Stefania Tamborini[4] and Michele Rossi[2,3,5]

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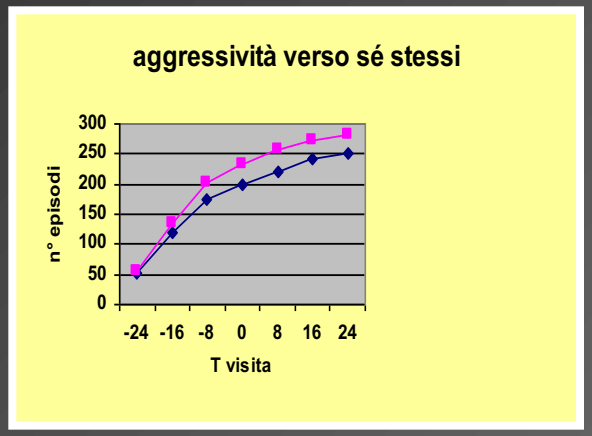
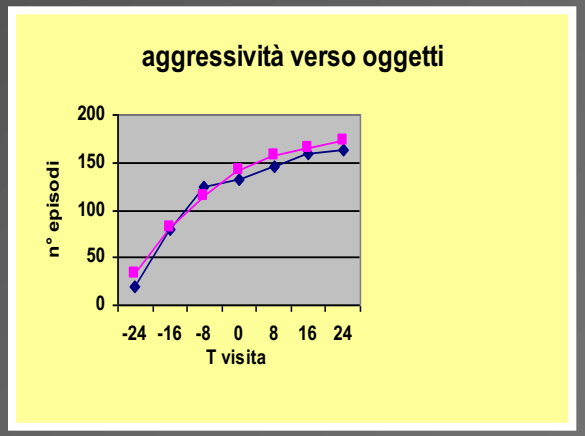
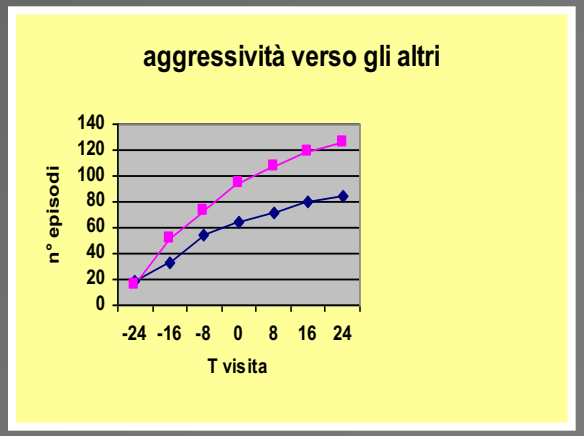
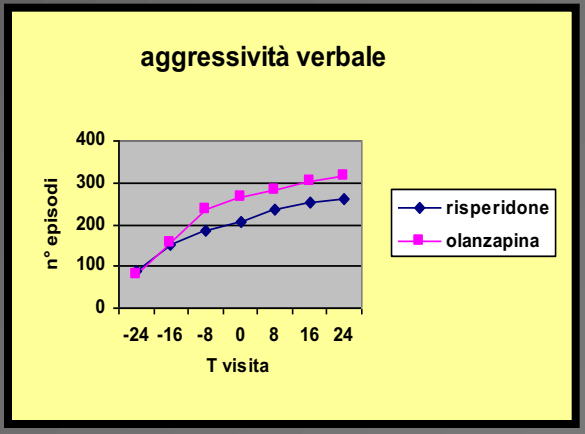
3. Operative Unit of Psychiatry, Department of Neurosciences, University of Florence, Florence (Italy)
4. Psychiatric Hospital, "Fondazione Sospiro", Cremona (Italy)
5. MAPPsi, Medics Associated for Psychiatry and Psychotherapy, Florence (Italy)









Journal of Intellectual Disability Research, 2011 Feb;55(2):210-8

Journal of Intellectual Disability Research

VOLUME 44 PART 2 pp 164–169 APRIL 2000

Use of the atypical antipsychotics Olanzapine and Risperidone in adults with intellectual disability

H. Williams, R. Clarke, N. Bouras, J. Martin & G. Holt

Estia Centre, York Clinic, Guy's Hospital, London, UK

- 2 naturalistic studies
- olanzapine more prescribed for psychosis
- risperidone more prescribed for problem behaviours associated with PD
- both resulted to be effective
- results limited by indirect assessment of PBs (through CGI)

Williams et al. 2000; Bokszanska et al. 2003

Research in Developmental Disabilities 31 (2010) 1135–1141

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Research in Developmental Disabilities

Review article

The use of clozapine among individuals with intellectual disability: A review

Ashvind N. Singh, Johnny L. Matson *, B.D. Hill, Russell D. Pella, Christopher L. Cooper, Angela D. Adkins

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Behavior problems

ABSTRACT

Clozapine has been approved in the United States since 1990 for refractory or treatment resistant schizophrenia in the general population. However, as with many other antipsychotic medications, it is being prescribed for reasons other than those indicated. Among individuals with intellectual disabilities, clozapine is increasingly being prescribed to treat behavioral problems, although the empirical evidence for such a practice is lacking. This review was undertaken as an attempt to summarize the available studies regarding the use of clozapine for behavioral purposes among individuals with intellectual disabilities. Findings of our review suggest that the effectiveness of clozapine in targeting challenging behaviors among individuals with intellectual disabilities is relatively inconclusive at present. We discuss reasons why these limitations exist and offer some solutions to help alleviate these limitations.

Contents

1. Introduction

Approved for use in the United States by the FDA in 1990, clozapine is an atypical antipsychotic medication prescribed for the treatment of psychosis associated with schizophrenia. Clinical trials and recent research indicate that clozapine is more

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Table 1
Summary of clozapine studies.

Author(s)	Sample					Controlled or crossover	Placebo	Blind	Free of other drugs	Inferential statistics	Drug/dose	Social/[cognitive changes][a]			Adverse effects
	Number	IQ	Age range	Level of ID	Misc. subject info										
Thalayasingam, Alexander, and Singh (2004)	24	Not reported	26–56	Borderline, mild and moderate		Retrospective analysis; data collected by chart review	No	No	Not reported	No	300–800 mg/day (mean = 485 mg/day)	↑ GI	Clinical Global Impressions (CGI) scale based on chart review		Drowsiness, weight gain, increased salivation, extrapyramidal symptoms (EPS), neutropenia
Hammock, Levine, and Schroeder (2001)	2	Not reported	44 and 53	Profound	Both nonverbal and aggressive	Controlled	No	Single	No	None	100–400 mg/day	↑ RS ↑ GI	?/4 aberrant behavior checklist (ABC)—subscales varied by individual Clinical Global Impressions (CGI) scale		Increase in dyskinesia symptoms as measured by the Dyskinesia Identification System Condensed User Scale (DISCUS)
Antonacci and de Groot (2000)	33	Not reported	23–55	Mild to severe		Retrospective analysis; data collected by chart review	No	No	No	None	75–600 mg/day	↑ GI	Clinical Global Impressions (CGI) scale		Constipation, tachycardia, hypotension, sedation, hypersalivation, incontinence
Kamal and Kelly (1999)	1	Not reported	32	Moderate	Case reports: aggressive and self-injurious	No	No	No	No	No	350 mg/day	↑ GI	Maladaptive behaviors according to staff report		Hypersalivation
Thuresson and Farnstrand (1999)	51	Not reported	*M* = 33	Mild to severe	Included in study if ever been treated with clozapine	Retrospective analysis; data collected by chart review	No	No	No	Inappropriate (frequency reports)	Not reported	↑ GI	Maladaptive behaviors according to staff report		Leukopenia, epileptic attacks, unpredictable aggressiveness, general emotional instability, hypersalivation, sedation, constipation
Buzan, Dubovsky, Firestone and Dal Pozzo (1998)	10	Not reported	20–63	Mild to profound		Retrospective analysis; data also collected by direct observation	No	No	No	Parametric (Student's *t*-test); probably OK	50–900 mg/day	↑ GI	Clinical Global Impressions (CGI) scale		Sedation, hypersalivation
												↑ GI	Global Assessment of Functioning (GAF)		

Hammock, Schroeder, and Levine (1995)	1	Not reported	40	Profound	Refractory self-injury	Crossover	Yes	Double	No	No	10–300 mg/day	↑ RS	4/4 aberrant behavior checklist (ABC) (stereotypy, hyperactivity, irritability, lethargy)	Seizures, hypersalivation, constipation, weight gain
												↑ GI	Maladaptive behaviors according to frequency counts	
Schroeder et al. (1995)	3	Not reported	34–43	Profound		Controlled	Yes	Double	No	No	300–475 mg/day	↑ RS	?/4 aberrant behavior checklist (ABC)—subscales varied by individual	Vomiting, drowsiness, agitation, weight gain, increased urinary frequency
												↑ GI	Maladaptive behaviors according to frequency counts	
Williams et al. (1995)	1	Not reported	4	Severe	17-year history of aggression and tantrums	No	No	No	After 14 months	Inappropriate (frequency reports)	500 mg/day	↑ GI	Maladaptive behaviors according to frequency counts	Not reported
Cohen and Underwood (1994)	6	Not reported	25–63	Moderate to profound	Case reports	No	No	No	No	Inappropriate (frequency reports)	500–600 mg/day	↑ GI	Maladaptive behaviors according to frequency counts	Hypersalivation, sedation, leukopenia, hypertension, sedation, weight gain
Pary (1994)	3	Not reported	29–64	Mild		No	No	No	No	None	200–400 mg/day	↑ GI	Maladaptive behaviors according to staff report	Extrapyramidal side effects (EPS), seizures
Sajatovic, Ramirez, Kenny, and Meltzer (1994)	5	VIQ M = 71.6 PIQ M = 64.8	M = 26.4	Borderline to mild		No	No	No	No	No	225–400 mg/day	↑ GI	Global Assessment Scale (GAS)	Sedation, hypotension, tachycardia, hypersalivation
Vyncke (1974)	40	36–59	M = 16.4	Mild to profound		No	No	No	No	Nonparametric (McNemar Test); OK	Varied by individual	↑ GI	Target behaviors and symptoms according to staff report	Tachycardia, sedation

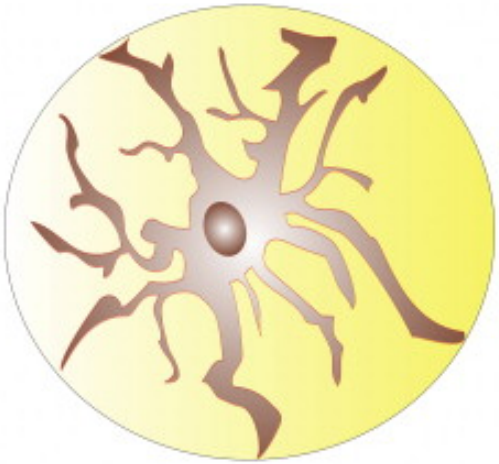
[a] Arrows indicate direction (↑: improvement, ↓: worsening, –: no change) of significant changes. GI: global impressions and RSL: rating scale. Detailed descriptions of categories are in the text. Ratios indicate the number of variables that changed significantly and the total number of variables measured. If cognitive changes were reported, other than in the form of standardized measures, they appear in the table in square brackets following the description of social changes.

CLOZAPINE

- mostly used for PBs
- some evidence of efficacy in case series
- efficacy on aggressivity, SIB, and disruptive behavior, even at low dose
- rare but relevant side effects (attention to neutropenia and seizures)

Janowsky DS et al., 2003; Singh AN et al., 2010; Zuddas et al., 2011

A **ASTROGLIA**



Neurogenesis

(Astrocytes are stem elements of neurogenic niches)

Synaptogenesis

Defining the cyto-architecture of the CNS

Formation of neuro-vascular unit and glial-vascular interface

Ion homeostasis

Water transport

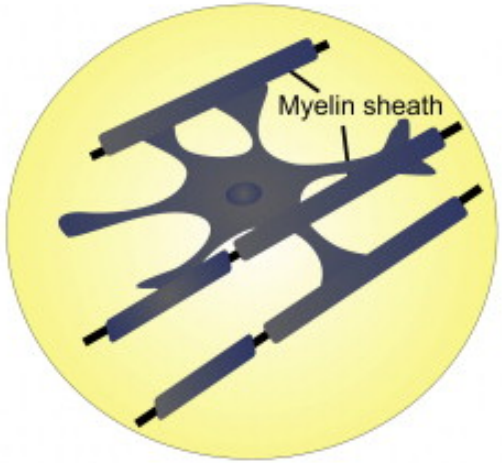
Neurotransmitter homeostasis

Synaptic maintenance and plasticity

Regulation of local blood flow

Chemoception

B **OLIGODENDROGLIA**



Myelination

Formation and maintenance of nodes of Ranvier

Clustering of ion channels at nodes

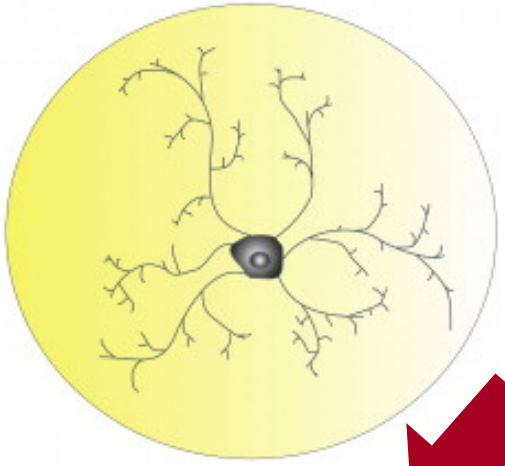
Saltatory conduction of action potentials

Minimisation of axonal diameter

Metabolic support of the axon

Mechanical support of the axon

C **MICROGLIA**



Clozapine and NGAs

Early synaptogenesis

Removal of redundant and malfunctional synapses

Fine tuning of synaptic ensembles

Secretion of trophic factors

Modulation of synaptic transmission

Regulation of neurogenesis

Kato TA, Myint AM, Steiner J. Editorial: Minding Glial Cells in the Novel Understandings of Mental Illness. Front Cell Neurosci. 2017 Feb 28;11:48.

Research in Developmental Disabilities 30 (2009) 613–669

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Research in Developmental Disabilities

Review

Practical guidelines for the use of new generation antipsychotic drugs (except clozapine) in adult individuals with intellectual disabilities

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ABSTRACT

New generation antipsychotic (NGA) drugs introduced to the US market after clozapine (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) are frequently used in individuals with intellectual disabilities (ID). However, there is very limited research to fully establish evidence-based or personalized medicine approaches for their use in this population. These guidelines take a pragmatic approach to establishing frameworks for their use by utilizing the prescribing information and reviewing the available literature on other relevant neuropsychiatric disorders. In the absence of expert consensus guidance and well-controlled comparison trials, we present a set of guidelines to inform initiation, dosing and monitoring of use in adults. Further, in these guidelines we provide practical information on drug–drug interactions and adverse drug reactions, and a brief review of discontinuation syndromes, potential for abuse, use during pregnancy and cost considerations. We also provide drug utilization review forms for each NGA to facilitate implementation of these guidelines, these guidelines provide a practical and necessary resource for practitioners treating psychiatric disorders and challenging behaviors in adult individuals with ID.

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Table 1
Most important available bibliography on the use of NGAs in individuals with intellectual disabilities (ID).

(A) NGAs in general

Aman and Madrid (1999) reviewed the use of NGAs in individuals with ID and later updated it (Aman & Gharabawi, 2004).

Cheng-Shannon, McGough, Pataki, and McCracken (2004) reviewed the use of NGAs in children and adolescents with some information on individuals with ID.

Friedlander, Lazar, and Klancnik (2001) conducted a chart review study focused on the use of NGAs for treatment in adolescents and young adults with ID.

Others reviewed the use of NGAs (Barnard, Young, Pearson, Geddes, & O'Brien, 2002; Masi, 2004) or pharmacological treatment in children and adolescents with ID (Hollander, Phillips, & Yeh, 2003; Palermo & Curatolo, 2004).

(B) Aripiprazole

Shastri, Alla, and Sabaratnam (2006) used aripiprazole for psychosis and behavioral disturbances in individuals with ID.

(C) Olanzapine

Aman and Gharabawi (2004) reviewed the use of olanzapine data in individuals with ID.

Janowsky, Barnhill, and Davis (2003) described using olanzapine in adults with ID.

(D) Quetiapine

Dobbs et al. (2004) studied thyroid disturbance in an adolescent with ID.

(E) Risperidone

Aman and Gharabawi (2004) provided specific risperidone dosing guidelines for individuals with ID.

Hellings et al. (2006) conducted a cross-over risperidone study in individuals with ID.

McCracken, McGough, and Shah (2002) conducted a prospective randomized placebo-controlled risperidone study in children with autism. There are additional articles from the same study (McDougle et al., 2005; Research Units on Pediatric Psychopharmacology Autism Network, 2005)

Singh, Matson, Cooper, Dixon, and Sturmey (2005) provided a critical view of the use of risperidone in individuals with ID.

West and Waldrop (2006) reviewed the use of risperidone in children with autistic disorders.

(F) Ziprasidone

Cohen, Fitzgerald, Okos, Khan, and Khan (2003) used ziprasidone to improve metabolic syndrome in adults with ID.

(G) Conventional and NGAs for aggression

Using the information from an attempt to discontinue conventional antipsychotics in 151 institutionalized individuals with ID treated in the 1990s, Janowsky et al. (2005, 2006) defend the idea of trying to establish the minimally effective dose of a conventional antipsychotic to treat aggression in each individual.

Tyrer et al. (2008) conducted a randomized placebo-controlled trial in adult outpatients with ID. Four weeks of treatment with placebo was associated with a decrease in aggressive behaviors, even more so than with risperidone and haloperidol treatments.

RISPERIDONE

- most studied among NGA
- more effective than TAPs on problem behaviours with lower extrapyramidal side effects.
- first choice drug for PBs in ID/IDD
- frequent hyperprolactinemia

Connor and Posever,1998. Advokat et al., 2000. La Malfa et al., 2006. Janowsky et al.,2003;

RISPERIDONE

approved for the treatment of i**rritability** associated with **autistic** disorder in children and adolescents (ages **5-16 years**), including symptoms of aggression, self-injury, tantrums, and quickly changing moods. It is the first prescription medication approved by the FDA for this purpose.

Higher efficacy with **topiramate** on irritability, hyperactivity, and stereotypic behaviour (RCT)[2]

Higher efficacy with **pentoxifylline**, **memantine**, and **celecoxib** on problem behaviours (RCTs)[3-5]

Frequent side effects: prolactine increase, increased appeteite, weight gain, and somnolence

1. Jesner et al. Risperidone for autism spectrum disorders [review]. Cochrane Database Syst Rev, 2007

2. Rezaei et al., 2010

3. Akhondzadeh et al., 2010; 4. Ghaleiha et al., 2013; 5. Asadabadi et al., 2013

PALIPERIDONE

Found to be generally well-tolerated and effective, but low evidence (1 open trial and few case reports)

Some advantages over risperidone in persons with hepatic impairment

side effects profile similar to risperidone: prolactine increase, increased appetite, weight gain, somnolence, tiredness

Stigler et al., 2010; Stigler et al., 2012; Kowalski et al., 2011

OLANZAPINE

- mostly used for PBs
- some evidence of efficacy in case series
- good efficacy on disorders different from schizofrenia, particularly mood disorders
- efficacy on aggressivity, SIB, and disruptive behavior
- good tolerability (attention to risk of metabolic disorders)

Janowsky DS et al., 2003; Singh AN et al., 2010; Zuddas et al., 2011

ARIPIPRAZOLE

is approved for the treatment of irritability associated with autistic disorder in children and adolescents (ages 6-17 years), including

- symptoms of aggression,
- self-injury,
- tantrums,
- quickly changing moods

Owen R et al. Pediatrics. 2009, Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder.

ARIPIPRAZOLE

prospective open label study, 12 weeks
12 young participants (6-25 aa) with FXS
daily mean dose: 9,8 mg

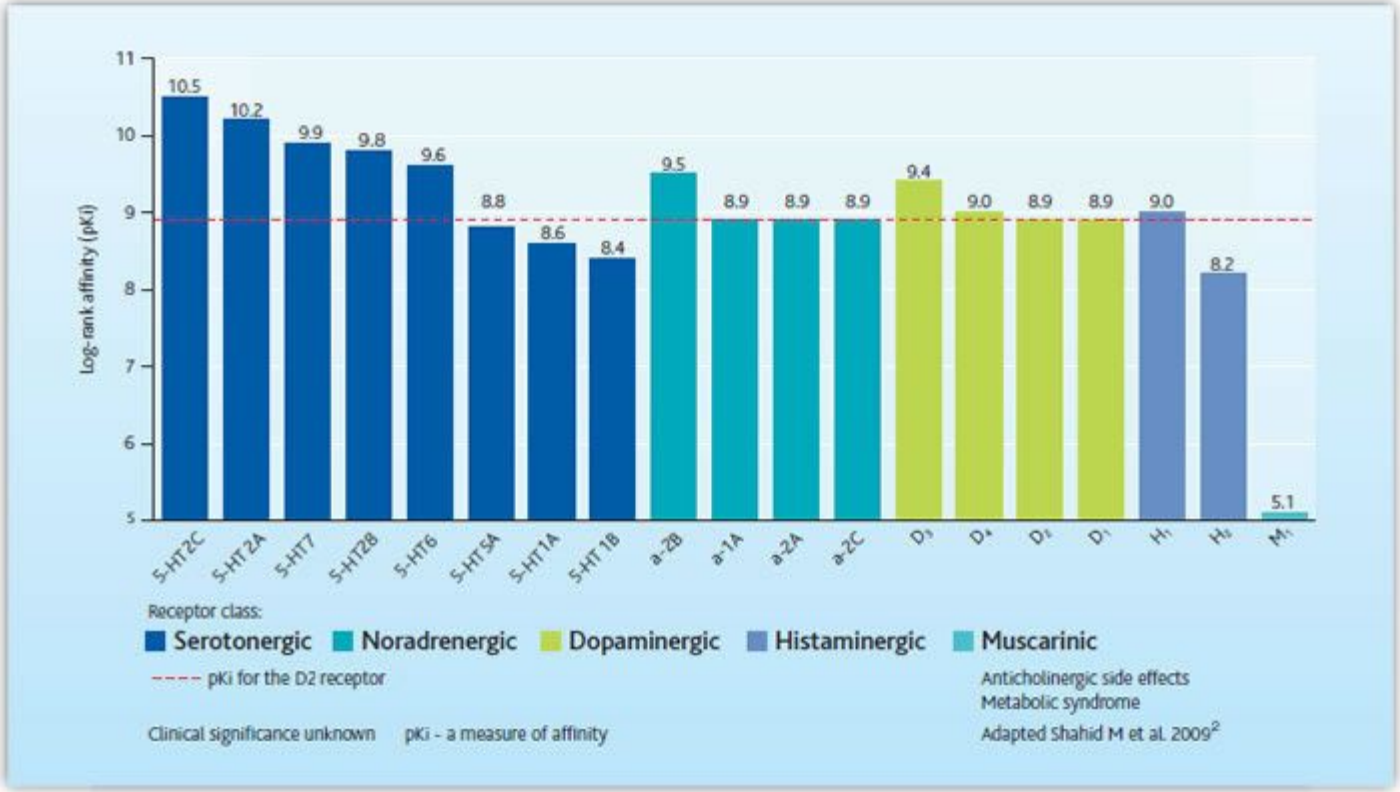
Significative improvement (CGI and ABC)

2 discontinuations:

- 1 for akathisia and tiredness
- 1 for tiredness

4 cases with psychotic disorder
1 case with PB and ASD
good efficacy and tolerability

Erickson CA et al., 2011; Shastri M. et al., 2006



Possible clinical effect

SEROTONERGIC
Anxiety, mood regulation, depressive and cognitive symptoms

DOPAMINERGIC
Psychotic, manic and cognitive symptoms

NORADRENERGIC
Depressive, psychotic and cognitive symptoms

HISTAMINERGIC
Somnolence and sedation

- No appreciable affinity for muscarinic receptors, unlike olanzapine and quetiapine[2]

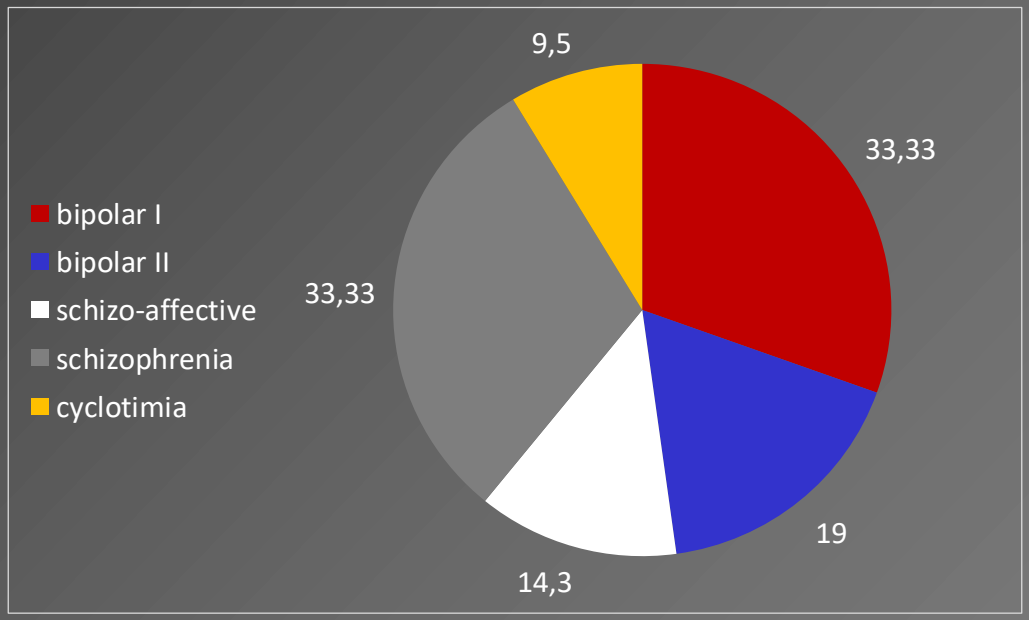
ASENAPINE

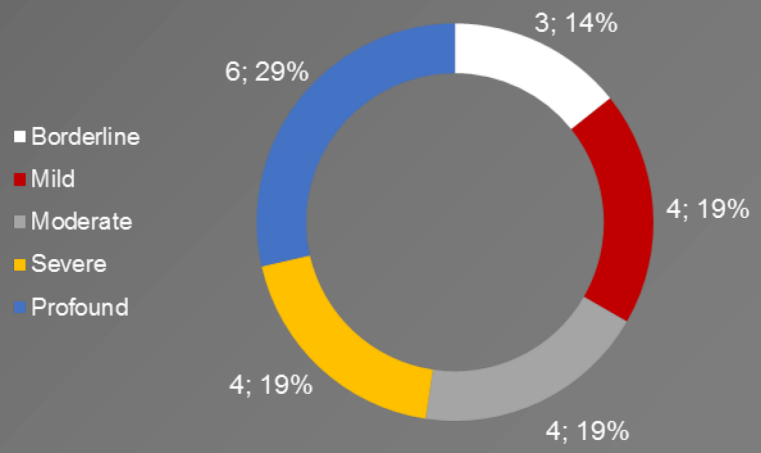
- 21 cases (26-45 yrs; ID from mild to moderate)
- 13 monotherapy; 8 in combination
- 7 drug naive, 14 switched from clozapine, olanzapine, valproate, clotiapine, delorazepam, clorpromazine, carbamazepine

ASENAPINE IN IDD: CASE SERIES

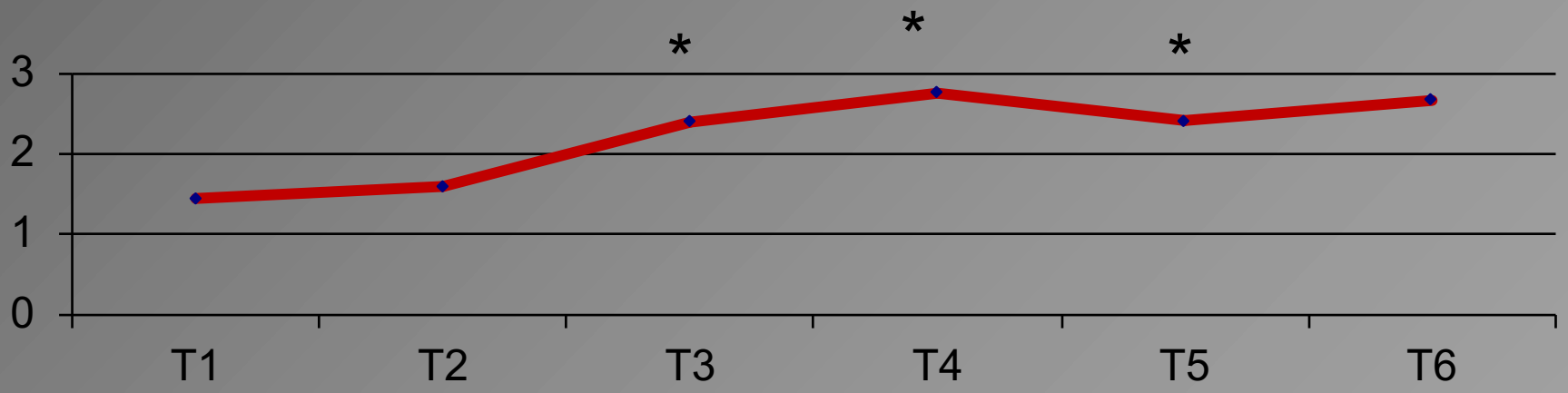
PROBLEM BEHAVIOUR	*N*	*%*
Aggressivity (towards others)	9	42,9
Self-injurious behaviour	6	28,6
hyperactivity	14	66,7
oppositive behaviour	11	52,4

N=21
Age 38.9 (14.8)

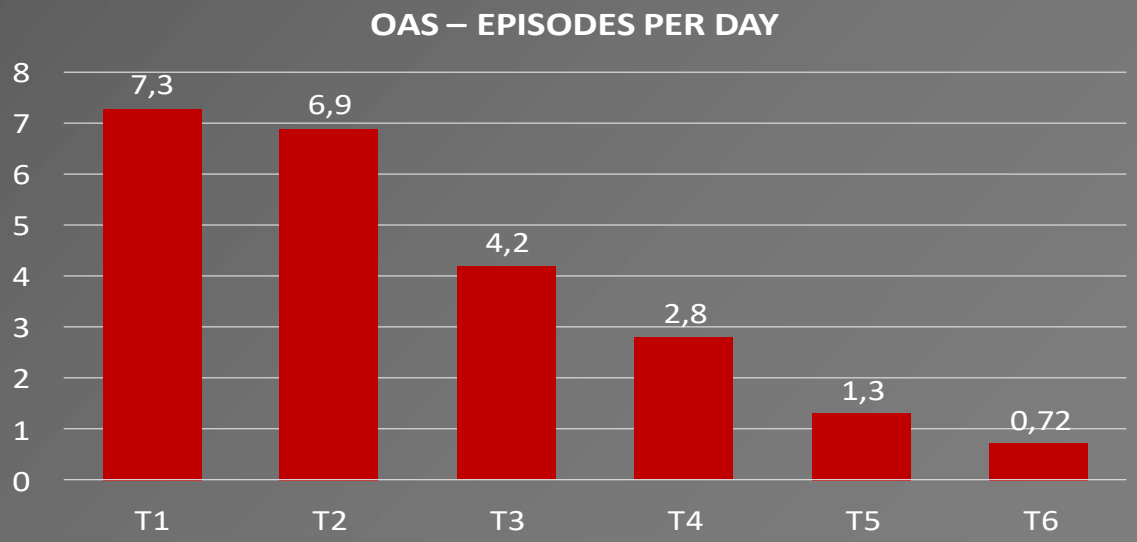




ASENAPINE IN IDD: CASE SERIES



* = p < 0,005; ** = p < 0,001



ASENAPINE IN IDD: CASE SERIES

SIDE EFFECTS			
TIME	N	N	%
B	21	15	71,4
T1	20	11	55,0
T2	20	12	60,0
T3	19	4	21,1
T4	17	4	23,5
T5	14	2	14,3
T6	6	1	16,7

After the first week side effects were recorded for 11 persons: 1 case with psycho-motor agitation and insomnia, 2 with sedation, headache, and ALT increase, 1 with hyperprolactinemia and sialorrhea, 3 with dizziness, 3 with affective flattening, 2 with nausea, 1 with motor slowness, and 1 with slowness and hypotension.

After the forth week only 4 participants still reported SE: hyperprolactinemia, sialorrhea, and ALT increase, but the all three were on polytherapy.

At T6 only 1 person still presented SE (sialorrhea).

clinical improvement (CGI at 1, 3, 6 months)

ZIPRASIDONE

- prevalent use on PBs
- some evidence of efficacy in case series
- good tolerability (weight neutral)

40 persons with ID and PB, overweight and dyslipidemia (total colesterol, HDL, LDL, TG)

- efficacy on PB
- weight and dyslipidemia improvement

Cohen S et al, 2003

OTHER NGA

CLOZAPINE

Only case reports, reported benefits

OLANZAPINE

reports of effectiveness, but no strong evidence

QUETIAPINE

reports of effectiveness, but no strong evidence

1. Owen R et al. Pediatrics. 2009,; 2. Sung et al., 2014; 3. Marcus et al., 2011; Ching & Pringsheim, 2012

INTERVENTO FARMACOLOGICO NELLA DI E NEL DdSA

HIGHLIGHTS SU STABILIZZATORI DELL'UMORE

MOOD STABILISERS - ANTIEPILEPTICS

DIVALPROEX SODIUM

irritability, aggression, compulsive behaviours[1-2]

LAMOTRIGINE

(inhibits glutamate release) – depression, anxiety

LEVETIRACETAM

1 open label study[3] showing improvement of aggression, mood instability (antidepressant?), other studies showing no efficacy on PBs[4]

1. Hellings et al., 2005; 2. Hollander et al., 2006; 3. Rugino, 2002; Wasserman et al., 2006

EFFECTS OF ANTIDEPRESSANTS ON LONGEVITY AND DEMENTIA ONSET IN DOWN SYNDROME

- retrospective study on 357 adults with Down syndrome
- The mean age at dementia onset among those receiving antidepressants before onset was 53.75 years versus 52.44 years among others (hazard ratio = 0.69; 95% CI, 0.48-0.98; P = .038)
- Mean age at death or at end of study for those receiving antidepressants was 54.71 years; among others, it was 52.60 years (hazard ratio = 0.63; 95% CI, 0.42-0.94; P = .024)

Tsiouris JA, Patti PJ, Flory MJ. Effects of antidepressants on longevity and dementia onset among adults with Down syndrome: a retrospective study. J Clin Psychiatry. 2014 Jul;75(7):731-7.

MEDICATION FOR ADHD

METHYLPHENIDATE

Large scale RCT, less effective than in ADHD alone, but recent slight shift (also communication, self regulation, and hyperactivity)[1-2]

risk of side effects (irritability, stereotypies, sleep disturbance) higher in ASD than in ADHD alone

lower doses with careful clinical monitoring

ATOMOXETINE

Large scale RCT, beneficial results on ADHD in persons with ASD

A recent review suggests higher efficacy on low severity of ASD[3]

1. Ghuman et al., 2009; Jahromi et al., 2009; 3. Ghanizadeh, 2013

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