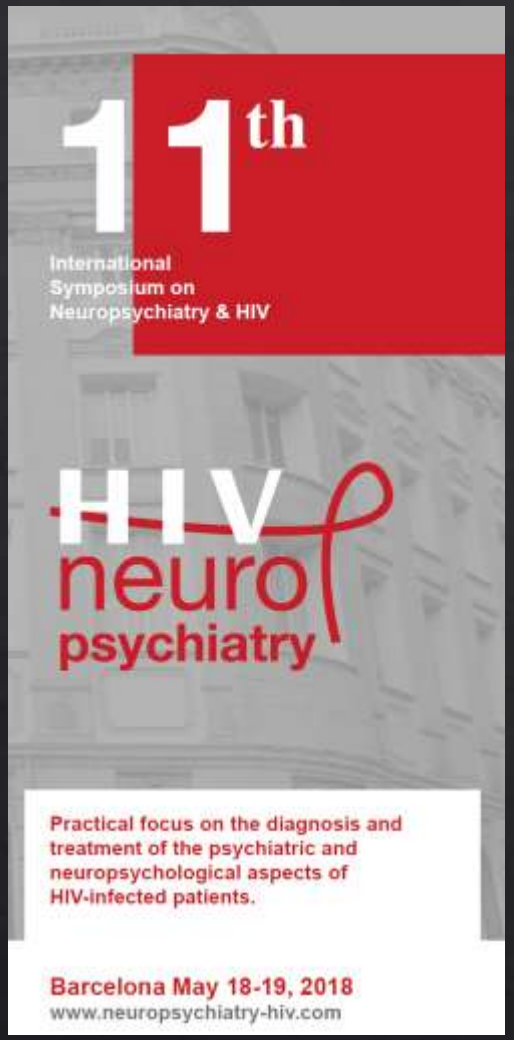

2. Neuropsychiatric disorders in HIV:
   - Scope of the problem. Milton Wainberg
   - Screening of Neurocognitive Diorders. Jose Muñoz-Moreno.
   - Diagnosis. Annemiek Shadé.
   - Treatment. Guida Da Ponte.

How to treat psychiatric disorders in HIV + individuals?

Guida da Ponte
Liaison Psychiatrist, MD
Medical School of Lisbon, University of Lisbon, Portugal
Department of Psychiatry and Mental Health, Centro Hospitalar Barreiro-Montijo, Barreiro, Portugal

No conflic of interest

General principles of prescribing in HIV+ individuals

- Start with a low dose and titrate according to tolerability and response;
- Select an agent with the fewest side-effects/interactions (medical comorbidity and drug interactions);
- Select the simplest dosing regime possible;
- Close collaboration with HIV physicians;

The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015; American Psychiatric Association, access April 29,2018

General principles of prescribing in HIV+ individuals

- Most psychotropic agents are thought to be safe in HIV+ individuals;
- HIV+ individuals may be more sensitive to higher doses, adverse side effects and interactions, specially if: low CD4 counts and high viral loads;
- In late-stage HIV disease:
  - High-potency AP (e.g. haloperidol) can be associated with severe side-effects, especially EPS (e.g. parkinsonism unresponsive to usual treatments) and rapid onset of NMS or tardive dyskinesia → use the lowest possible doses;
  - Select atypical AP;

AP: antipsychotics; EPS: extrapyramidal symptoms;
NMS: neuroleptic malignant syndrome

The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015; American Psychiatric Association, access April 29,2018

General principles of prescribing in Depression

- The same treatments used in general population are effective, *but* consider stage of illness and treatment plan;
- Moderare to severe depression → 1st line: SSRI: escitalopram/citalopram;
- Duration of treatment: 6–9 months if single episode (2 years*);
- Withdraw AD gradually;

- TCAs may be appropriate in some cases, but side effects may limit efficacy and compliance;
- MAOIs NOT recommended;
- Other agents (bupropion, mirtazapine, trazodone) are not recommended for routine use → side effects;
- Stimulants have been successfully used;

AD: antidepressants; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclis; MAOI: monoamine oxidase inhibitor; *if two prior episodes + functional impairment;

DeSilva et al., 2001; Anon, 2002; Portegies et al., 2004; NICE guidelines 2007; Freudenreich et al., 2010; American Psychiatric Association, access April 29,2018

Treatment of Depression

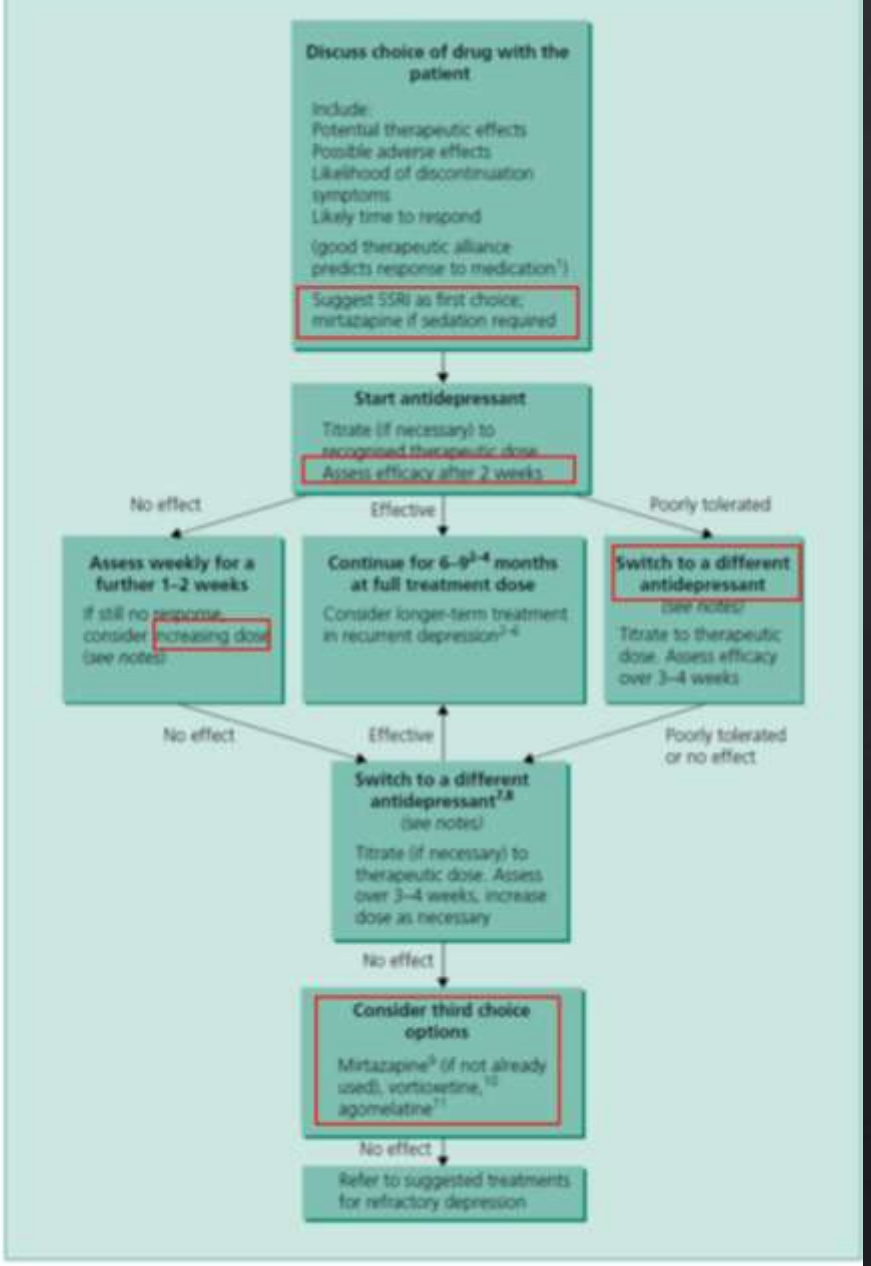

Figure 4.1 Drug treatment of depression. SSRI, selective serotonin reuptake inhibitor.

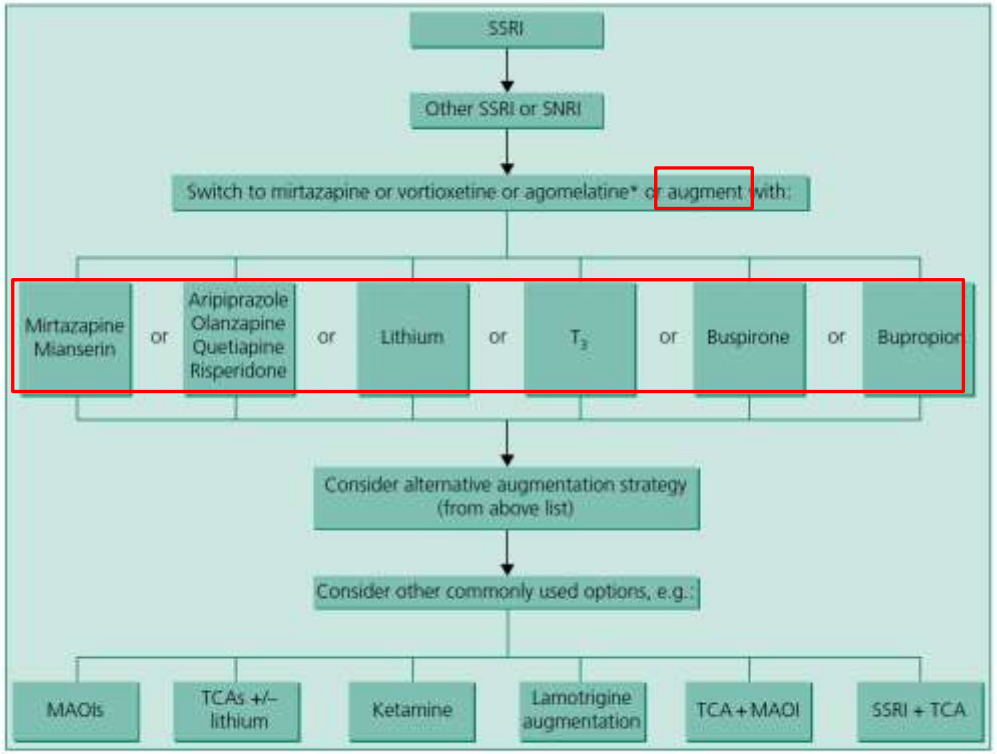

Figure 4.3 Treatment sequence options for refractory depression.
*Some may consider the closely supervised use of older antidepressants – TCAs (e.g. amitriptyline or nortriptyline) or MAOIs (e.g. phenelzine) at this point. MAOI, monoamine oxidase inhibitor; SNRI, selective noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015

Adverse effects and doses of antidepressants

Tabla 2
Resumen del manejo de los antidepresivos

	Dosis diaria (mg)[a]	Efectos adversos[b] y especificaciones
Inhibidores selectivos de la recaptación de serotonina (ISRS): aumentan la disponibilidad de serotonina		
Fluoxetina	10 a 60	De primera elección[3,4,7]. Preferiblemente citalopram y escitalopram, debido a su débil acción sobre el sistema del citocromo P450. En general, buena tolerancia. Precaución síndrome serotoninérgico, especialmente con fluoxetina y fluvoxamina en combinación con inhibidores de la proteasa
Paroxetina	10 a 50	
Citalopram	10 a 60	
Escitalopram	5 a 30	
Sertralina	50 a 200	
Fluvoxamina	50 a 200	
Tricíclicos: aumentan la disponibilidad de serotonina y de noradrenalina; también tienen diferentes mecanismos de acción sobre otros receptores		
Imipramina	25 a 300	*Efectos anticolinérgicos* relevantes (sequedad de boca, retención urinaria, visión borrosa, etc.) que interfieren en el cumplimiento del tratamiento[3,4]. Alteraciones ECG
Nortriptilina	25 a 200	
Clomipramina	75 a 200	
Otros		
Mirtazapina	15 a 45	*Sedación* y hiperorexia (pueden ser beneficiosos en algunos pacientes)[8]. Tiene mucha menor afectación sobre la función sexual que otros antidepresivos. Aumenta la disponibilidad de serotonina y noradrenalina, mediante el bloqueo el receptor presináptico (autorreceptor)
Venlafaxina	75 a 375	*Náuseas, sequedad de boca, somnolencia*, estreñimiento, hipertensión. Inhibe la recaptación de serotonina y de noradrenalina, por lo que suele ser más eficaz que los ISRS en el tratamiento de la depresión. También tiene indicación para el tratamiento de la ansiedad
Desvenlafaxina	50 a 200	*Náuseas*. Es el metabolito activo de la venlafaxina, con menos interacciones que la anterior[9]
Duloxetina	40 a 120	*Náuseas, sequedad de boca, nerviosismo, insomnio*, estreñimiento, hiporexia
Trazodona	100 a 300	*Sedación, sequedad de boca*, vértigo Con un perfil similar a la mirtazapina, se suele utilizar como hipnótico
Bupropión	150 a 300	*Insomnio, dolor de cabeza, náuseas, sequedad de boca*, estreñimiento, nerviosismo e hiporexia. Efecto activador, inhibiendo la recaptación de dopamina. Indicado en pacientes con anergia[10]. Riesgo de diminuir el umbral convulsivo y de provocar síntomas psicóticos[11]
Agomelatina	25 a 50	*Riesgo de hepatotoxicidad*. Tiene un mecanismo de acción particular. Es melatoninérgico y también noradrenérgico y dopaminérgico. No afecta la función sexual. Dado su riesgo de toxicidad hepática hay que realizar control de transaminasas cada 3, 6, 12 y 24 semanas al iniciar el tratamiento o al aumentar la dosis[12]

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HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

Pharmacokinetic interactions of antidepressants with CYP

Substrates, inhibitors	1A2	2C9	2C19	2D6		3A4,5,7	
	Amitriptyline	Amitriptyline	Diazepam	Tamoxifen	Atomoxetine	BZD*	Haloperidol
	Clomipramine	Fluoxetine	Amitriptyline	Amitriptyline	Thioridazine	Indinavir. Nelfinavir, Ritonavir, Saquinavir	Methadone
	Clozapine	Valproic acid	Citalopram	Clomipramine	Zuclopenhixol	Aripiprazol	Nevirapine
	Duloxetine		Clomipramine	Desipramine	Amphetamine	Buspirone	Pimozide
	Fluvoxamine		Imipramine	Fluoxetine	Chlorpromazine	Carbamazepine	Quetiapine
	Haloperidol		Nelfinavir	Imipramine	Donepezil	Cocaine	Risperidone
	Olanzapine			Paroxetine	Duloxetine	Trazodone	Ziprazidone
				Venlafaxine	Fluvoxamine		
				Haloperidol	Nortriptyline		
				Chlorpromazine	Promethazine		
				Tramadol	Risperidone		
				Aripiprazol	Bupropion		
					Sertraline		

*alprazolam, diazepam, midazolam, triazolam, zolpidem; AUC: area under the plasma concentration versus time curve; Strong inhibitor: > 5-fold ↑ in the plasma AUC values or > 80% ↓ in clearance; Moderate inhibitor: > 2-fold ↑ in the plasma AUC values or 50-80% ↓ in clearance;

http://medicine.iupui.edu/CLINPHARM/ddis/main-table; http://www.interaccionesvih.com/

Antidepressants and QTc prolongation

Table 2. Psychiatric Drugs With a Higher Risk of QTc Prolongation at Therapeutic Doses

Drug Class	Drug Name
Typical antipsychotics	Thioridazine, haloperidol, chlorpromazine, pimozide
Atypical antipsychotics	Ziprasidone, iloperidone, quetiapine
SSRIs	Citalopram, escitalopram
TCAs and TeCAs	Amitriptyline, imipramine, maprotiline, nortriptyline, desipramine, clomipramine, trimipramine
SNRIs	Venlafaxine
Other antidepressants	Mirtazapine

QTc: corrected QT; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant.
Source: References 2-12, 14-18, 24.

Table 3. Psychiatric Drugs With a Lower Risk of QTc Prolongation at Therapeutic Doses

Drug Class	Drug Name
Typical antipsychotics	Loxapine
Atypical antipsychotics	Olanzapine, risperidone, paliperidone, aripiprazole, asenapine, clozapine, brexpiprazole, lurasidone
SSRIs	Paroxetine, fluoxetine, sertraline, fluvoxamine
TCAs and TeCAs	Doxepin
SNRIs	Duloxetine, desvenlafaxine, levomilnacipran, milnacipran
Other antidepressants	Bupropion, vortioxetine, vilazodone, trazodone

QTc: corrected QT; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant.
Source: References 3-6, 8, 9, 13, 17-23, 25-27.

Dietle 2015

Psychostimulants in Depression

- ≠ AD:
  - ↓ fatigue, promote wakefulness and mood elevating;
  - Effects within few hours;
- Amfetamines and methylphenidate:
  - Propensity for tolerance and dependence → useful when a prompt effect is required + dependence is not a problem (e.g. terminal illness);
  - If prolonged use of high doses: paranoid psychosis;
- Modafinil:
  - Adjunct to standard AD, specially if hypersomnia and fatigue;
  - No tolerance, dependence or psychosis but lacks the euphoric effects of amphetamines;.

Monotherapy or add-on treatment in late-stage terminal cancer	Methylphenidate 5–30 mg/day[31–35] Dexamfetamine 2.5–20 mg/day[36,37] Methylphenidate 20 mg/day + mirtazapine 30 mg/day[38]	Case series and open prospective studies Beneficial effects seen on mood, fatigue and pain RCT shows benefit for combination from third day of treatment	Useful treatment options in those expected to live only for a few weeks. Best reserved for hospices and other specialist units
Monotherapy in depression secondary to medical illness	Methylphenidate 5–20 mg/day[46] Dexamfetamine 2.5–30 mg/day[47,48]	Limited data	Psychostimulants now not appropriate therapy. Standard antidepressant preferred
Monotherapy in depression and fatigue associated with HIV	Dexamfetamine 2.5–40 mg/day[49,50]	Supported by one good, controlled study[50] Beneficial effect on mood and fatigue	Possible treatment option where fatigue is not responsive to standard antidepressants
Adjunctive treatment of depression with fatigue and hypersomnia	SSRI + modafinil 200 mg/day[15,16] SSRI + methylphenidate 10–40 mg/day[17]	Beneficial effect only on hypersomnia. Modafinil may induce suicidal ideation Clear effect on fatigue in hospice patients	Possible effect on fatigue, but weak evidence base. An option where fatigue is prominent and otherwise unresponsive

AD: antidepressants;

Menza el al., 2000; Goss et al., 2013; *Adapted from:* The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015

General principles of prescribing in Anxiety

- 1st line: SSRIs (sertraline) in GAD, social fobia, OCD and PTSD;
  - Efficacy → 12 weeks;
  - Duration of treatment: at least 6 months;
- If complex anxiety disorders refractory to treatment → psychological + pharmacological therapies;
- Gabapentine and pregabaline : low risk drug-drug interactions;
- Some evidence for buspirone;

SSRI: selective serotonin reuptake inhibitors; GAD: generally anxiety disorder; OCD: obsessive compulsive disorder; PTSD: post traumatic stress disorder;

Batki et al., 1998; Freudenreich et al., 2010; National Institute for Health and Clinical Excellence, 2005, 2011; Grupo de Expertos de la Secretaría del Plan Nacional Sobre el Sida (SPNS), Sociedad Espa˜nola dePsiquiatría (SEP), Grupo de Estudio de Sida (GESIDA) y Sociedad Espa˜nola de Infectología Pediátrica(SEIP), 2015;; American Psychiatric Association, access April 29,2018

General prescribing in Anxiety

- Benzodiazepines:
  - All guidelines and consensus statements recommend: only use to treat anxiety that is severe, disabling or subjecting the individual to extreme distress *(do not deny treatment);*
    - Lowest effective dose for the shortest period of time (maximum 4 weeks);
  - Potential to cause physical dependence and withdrawal symptoms → caution if substance misuse;

Table 4.24 Switching from benzodiazepines to diazepam: doses

Benzodiazepine	Approximate dose (mg) equivalent to 10 mg diazepam
Chlordiazepoxide	25 mg
Clonazepam	1–2 mg
Lorazepam	1 mg
Lormetazepam	1 mg
Nitrazepam	10 mg
Oxazepam	30 mg
Temazepam	20 mg

Nash et al., 2005; Davidson, 2006; Martin et al., 2007; National Institute for Health and Clinical Excellence, 2011

General principles of prescribing in Bipolar disorder

- Refer to psychiatrist;
- Higher sensibility to side-effects of mood stabilizers such as lithium, especially if neurocognitive dysfunction → limit use for asymptomatic individuals with higher CD4 counts and monitor closely;
- Valproate, lamotrigine and gabapentin may be used cautiously;
- Avoid carbamazepine → important interactions and risk of neutropenia;
- Option: use of antimanic antipsychotics – risperidone, quetiapine, olanzapine;

Parenti et al., 1998; Berbel et al., 2000; Freudenreich et al., 2010; Grupo de Expertos de la Secretaría del Plan Nacional Sobre el Sida (SPNS), Sociedad Espa˜nola dePsiquiatría (SEP), Grupo de Estudio de Sida (GESIDA) y Sociedad Espa˜nola de Infectología Pediátrica(SEIP), 2015;

General principles of prescribing in Psychotic disorders

- Consider differential diagnosis: physical, pharmacological → *delirium;*
- *Agitated delirium* → 1st line: haloperidol, risperidone;
- *Functional* psychosis → 1st line: atypical AP – risperidone, quetiapine, aripiprazole, olanzapine, paliperidone (adverse effect profile and relative toxicity);
  - Paliperidone as 1st line;
  - Olanzapine or risperidone may be better options than quetiapine;
  - Clozapine is not routinely recommended:
    - Useful in low doses in patients medically stable with > CD4 counts, and HIV-associated psychosis with drug-induced parkinsonism;
    - Close monitoring of WCC (higher risk of agranulocytosis?);

WCC: white cell count; AP: antipsychotics;

Lera et al., 1999; Jover et al., 2002; Freudenreich et al., 2010; Grupo de Expertos de la Secretaría del Plan Nacional Sobre el Sida (SPNS), Sociedad Espa˜nola dePsiquiatría (SEP), Grupo de Estudio de Sida (GESIDA) y Sociedad Espa˜nola de Infectología Pediátrica(SEIP), 2015;

Antipsychotics: doses and adverse effects

Table 2.7 Relative adverse effects of antipsychotic drugs

Drug	Sedation	Weight gain	Akathisia	Parkinsonism	Anti-cholinergic	Hypotension	Prolactin elevation
Amisulpride	–	+	+	+	–	–	+++
Aripiprazole	–	–	+	–	–	–	–
Asenapine	+	+	+	–	–	–	+
Benperidol	+	+	+	+++	+	+	+++
Chlorpromazine	+++	++	+	++	++	+++	+++
Clozapine	+++	+++	–	–	+++	+++	–
Flupentixol	+	++	++	++	++	+	+++
Fluphenazine	+	+	++	+++	++	+	+++
Haloperidol	+	+	+++	+++	+	+	++
Iloperidone	–	++	+	+	–	+	–
Loxapine	++	+	+	+++	+	++	+++
Lurasidone	+	–	+	+	–	–	+
Olanzapine	++	+++	+	–	+	+	+
Paliperidone	+	++	+	+	+	++	+++
Perphenazine	+	+	++	+++	+	+	+++
Pimozide	+	+	+	+	+	+	+++
Pipothiazine	++	++	+	++	++	++	+++
Promazine	+++	++	+	+	++	++	++
Quetiapine	++	++	–	–	+	++	–
Risperidone	+	++	+	+	+	++	+++
Sertindole	–	+	–	–	–	+++	–
Sulpiride	–	+	+	+	–	–	+++
Trifluoperazine	+	+	+	+++	+	+	+++
Ziprasidone	+	–	+	–	–	+	+
Zuclopenthixol	++	++	++	++	++	+	+++

+++ high incidence/severity, ++ moderate, + low, – very low.

Manejo de los antipsicóticos

	Dosis diaria (mg)[a]	Efectos adversos[b] y especificaciones
Antipsicóticos típicos		
Haloperidol	VO: 0,5 a 20 (máximo 50) IM: 40 (máximo 120) Repartida en 2 a 4 tomas.	Más tendencia a los *efectos adversos extrapiramidales* (hipocinesia, rigidez, distonía), especialmente con el haloperidol, la flufenazina y la trifluoperazina
Perfenazina	VO: 2 a 24, repartida en 3 tomas.	
Trifluoperazina	VO:2 a 24 repartido en 2 a 3 tomas.	
Flufenazina	IM: 12,5 a 50 de una a cuatro tomas semanales	
Clorpromazina	25 a 150	Más tendencia a los *efectos anticolinérgicos* con la clorpromazina y la perfenazina
Antipsicóticos atípicos		
Clozapina	25 a 450	
Olanzapina	2,5 a 20	
Quetiapina	100 a 800	
Ziprasidona	40 a 160	
Risperidona	0,5 a 6	
Paliperidona	3 a 12	
Aripiprazol	15 a 30	

[a] Los individuos de edad avanzada requ… aplicarse las recomendaciones especificad…

[b] Listado no exhaustivo. Se indican en …

Table 2. Psychiatric Drugs With a Higher Risk of QTc Prolongation at Therapeutic Doses

Drug Class	Drug Name
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SNRIs	Venlafaxine
Other antidepressants	Mirtazapine

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The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015; Grupo de Expertos de la Secretaría del Plan Nacional Sobre el Sida (SPNS), Sociedad Espa˜nola dePsiquiatría (SEP), Grupo de Estudio de Sida (GESIDA) y Sociedad Espa˜nola de Infectología Pediátrica(SEIP), 2015; Dietle 2015; www.crediblemeds.org

Thanks for your attention

guidadaponte@gmail.com

Treatment of Bipolar disorder

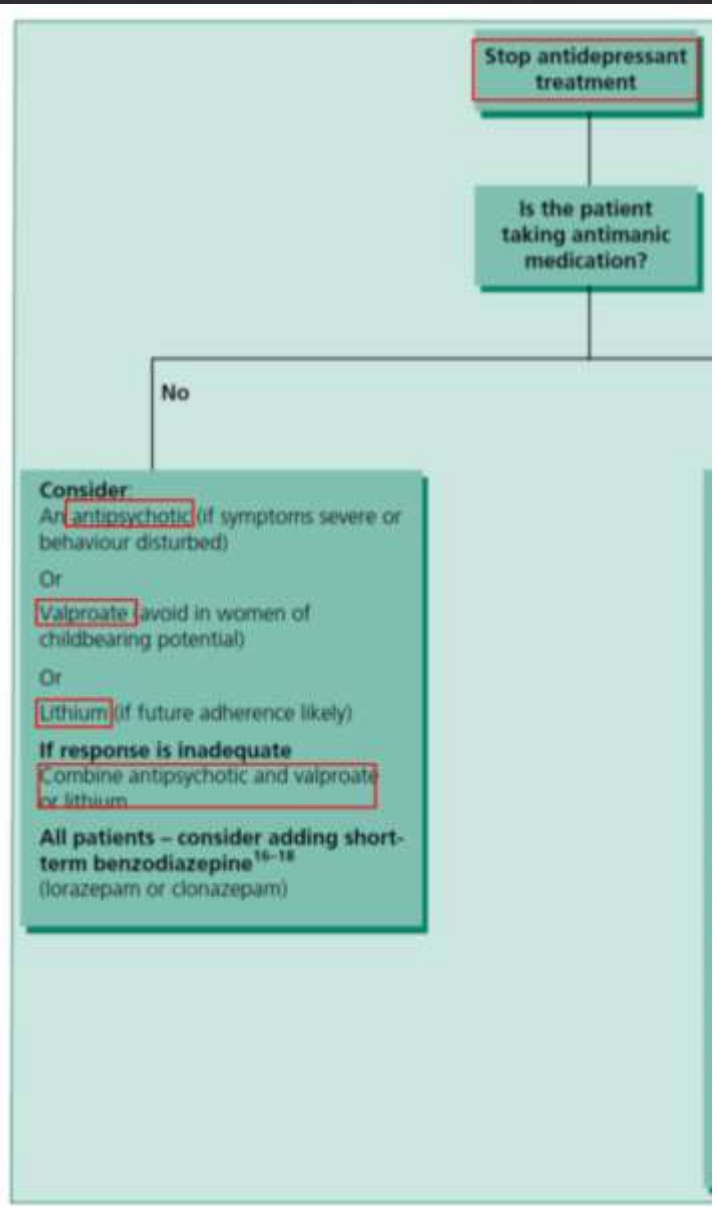

Figure 3.1 Treatment of acute mania or hypomania.[2–15] Note that lithiur states[21] or substance misuse.[22]

Tabla 4
Estabilizadores del humor

	Dosis diaria (mg)	Efectos adversos y especificaciones
Carbonato de litio	Mantener concentraciones (0,6 a 1,0 mEq/l)	Temblor, poliuria, polidipsia, diarrea, aumento de peso, alteraciones ECG. No requiere metabolismo hepático, por lo que es una opción razonable para pacientes que reciben fármacos antirretrovirales[18,19]. Requiere monitorización de niveles plasmáticos, de función renal y función tiroidal con regularidad (cada 6-12 meses). Riesgo de neurotoxicidad, a pesar de niveles plasmáticos adecuados. Es preferible evitar pacientes con manía secundaria al VIH o en fases avanzadas de la infección por el VIH
Valproato	Mantener concentraciones (40 a 100 µg/ml)	Náuseas, vómitos, diarrea, estreñimiento, aumento de peso, temblores, ataxia, somnolencia, cefalea, aplasia medular, hepatitis. Especialmente indicado en pacientes que desarrollen una manía secundaria al virus o al consumo de sustancias psicoactivas. Aumenta la replicación vial mediante un mecanismo indeterminado. Puede tener un efecto protector frente a los síntomas neurológicos del sida[20]
Carbamazepina	Mantener concentraciones (4 a 10 µg/ml)	Aplasia medular, agranulocitosis, mareo, vértigo, cefalea, visión borrosa, náuseas y vómitos (menos frecuentes si se inicia la terapia con dosis progresivas), ataxia y hepatitis. Se utiliza poco en pacientes VIH+, dado su riesgo de complicaciones medulares, como la leucopenia o la anemia aplásica y su potente efecto inductor enzimático[21,22]
Lamotrigina	100-400 mg/día (1 o 2 veces al día)	Eficaz para la prevención de las fases depresivas del trastorno bipolar[23]. Ha mostrado eficacia y buena tolerancia en el tratamiento del dolor neuropático en pacientes VIH

The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015; Grupo de Expertos de la Secretaría del Plan Nacional Sobre el Sida (SPNS), Sociedad Espa˜nola dePsiquiatría (SEP), Grupo de Estudio de Sida (GESIDA) y Sociedad Espa˜nola de Infectología Pediátrica(SEIP), 2015;

Treatment of *delirium*

- 1st line: AP
  - Except: alcohol, BZD abstinence
  - ECG: baseline, follow-up
    - QTc > 450 msec or > 25% baseline
      - Cardiology *and* ↓ dose *or* descontinue
  - 1st line: **haloperidol**
    - Less anticholinergic effects, metabolites, sedation
    - IV, IM, per os (IV → Qtc prolongation dose dependent)
    - Dose according to necessary: 0.25 - 0.5 mg qd/bid
  - Atypical AP:
    - If haloperidol in high doses *or* side effects

Antipsychotics commonly used in treating the symptoms of delirium:

Medication	Suggested initial dosage
[redacted]	
Risperidone	0.25 mg po od-bid
Olanzapine	1.25 mg - 2.5 mg po od
Quetiapine	12.5 mg - 50 mg po od

AP: antipsychotics; BZD: benzodiazepines;

American Psychiatric Association, 2004; Canadian Coalition for Seniors' Mental Health, 2006; Cochrane, 2009

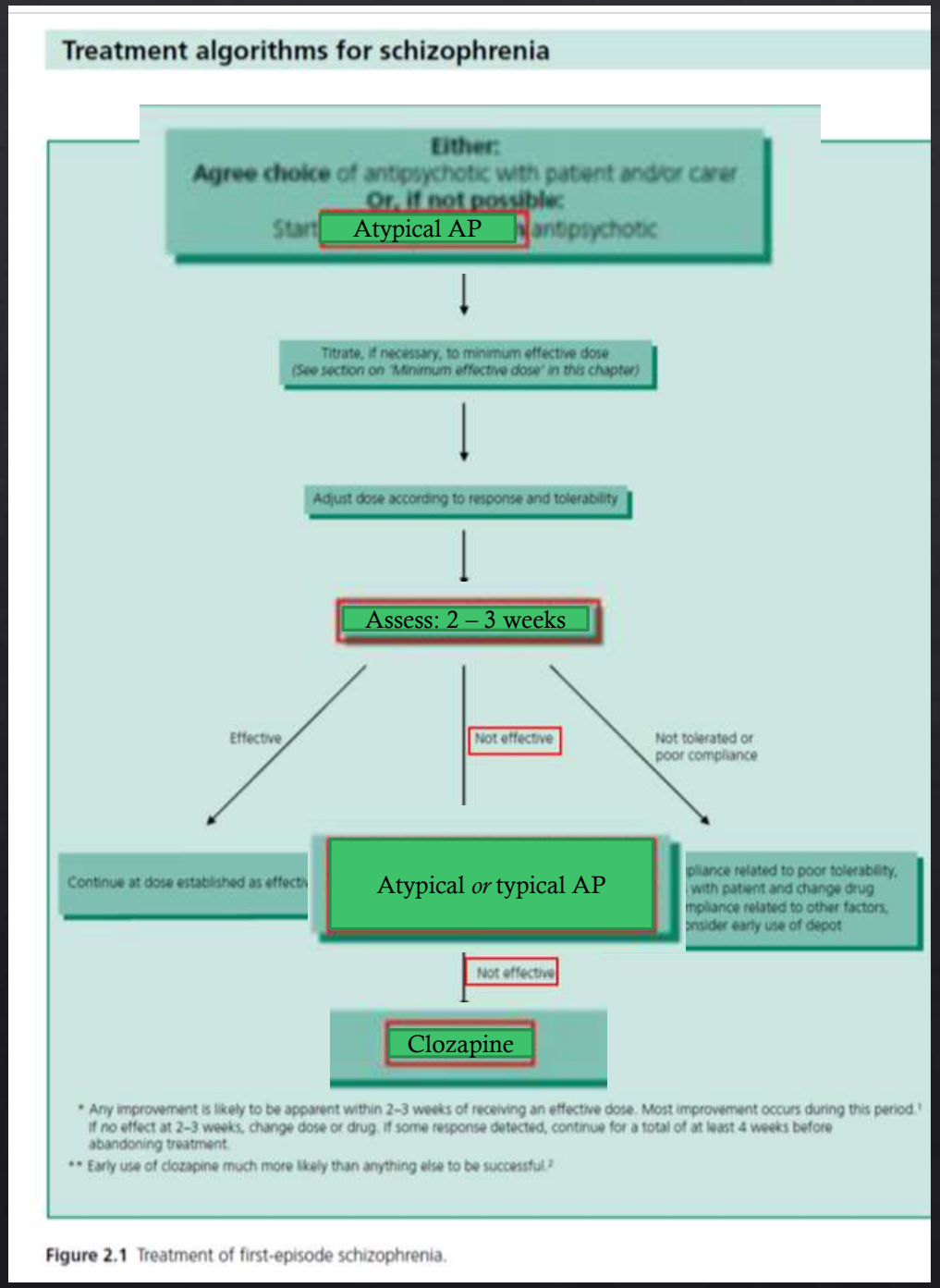

Figure 2.1 Treatment of first-episode schizophrenia.

Treatment *functional* psychosis

Tarsy D et al., 2011; Agid O et al., 2011; Leucht S et al., 2009, 2013;
The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015

Substance use

- Role of general physician → Detect substance use and refer to specialized centers (ideal treatment setting treats both diseases in an integrated form);

- Main goals:
  - ↓ or ∅ drug use;
  - Sustain reduction of high-risk behaviors;
  - Long-term: develop the ability to quickly control relapse and maintain the positive behaviors learned in treatment;

- The treatment should be individualized, combining several strategies (counseling, individual psychotherapy / socio-familiar and pharmacological);

- Generally: outpatient treatment → if ineffective → residential treatment;

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Substance use treatment

- Main treatments are based on psychological therapies and individual, group and socio-family support;
- Standard pharmacological treatments for rehabilitation: disulfiram, naltrexone, acamprosate, buprenorphine, methadone;
  - Long-term Methadone Maintenance Therapy (MMT) → if severe substance dependence;
- Pharmacological treatment has been shown to be effective primarily for alcohol and opioid dependence;

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Alcohol – Relapse prevention

Acamprosate

- Glutamatergic NMDA antagonist; ↑ GABAergic function;
- **Relapse prevention in moderate - severe dependence**;
- Duration of treatment: 6 months (longer if benefit); Dose: 1998 mg/day (666 mg 3 times/ day) if >60 kg *or* 1332 mg/day if < 60 kg;
- **Stop treatment if continuous drinking for 4–6 weeks;**

Naltrexone

- Non-selective opioid receptor antagonist → ∅ ↑ dopaminergic activity after consumption → ∅ reward;
- **↓↓↓ reduces relapse but does not necessarily improve continuous abstinence;**
- Dose: 50 – 100 mg/day; Duration of treatment: 6 months;
- Well tolerated*; It can be started when drinking or during medically-assisted withdrawal;

Nalmefene

- Opioid antagonist;
- **↓ heavy drinking days but does not promote abstinence;**
- **Inconclusive evidence in relapse prevention;**

Disulfiram

- Aldehyde dehydrogenase inhibition → acetaldehyde accumulation after alcohol → unpleasant physical effects (arrhythmias, hypotension, collapse) →→→ CI to use** / Supervision;
- **2nd line for moderate severe dependence if not suitable for acamprosate or naltrexone *or* preference for disulfiram (weaker evidence than acamprosate, naltrexone);**
- No consumption of alcohol for at least 24 hours before treatment;
- Doses: 800 mg1st dose, reducing to 100–200mg/day for maintenance;

CI: contraindicated; *side-effects; nausea, headache, abdominal pain, ↓ appetite, tiredness, hepatotoxicity;
**cardiac failure, coronary artery disease, hypertension, history of cerebrovascular disease, pregnancy, breast feeding, liver disease, peripheral neuropathy, severe mental illness;

Karhuvaara et al., 2007; NICE Clinical Guideline, 2011; Lingford-Hughes et al., 2012; van den BW et al., 2013;

Alcohol withdrawal

- BZD for 7 days (longer if *delirium tremens*) – choice:
  - Chlordiazepoxide: uncomplicated withdrawal;
  - Shorter-acting (lorazepam, oxazepam): alcoholic liver disease;
  - Longer-acting: prevention of seizures and delirium;
- Mode of administration:
  - "front-loading": loading dose → doses/≈ 90 minutes → light sedation;
  - Symptom-triggered therapy;
  - Tappering dose regímen;
- Wernicke's encephalopathy: Thiamine IM/day (prophylaxis: 200–300 mg; treatment: > 1200 mg);

	Chlordiazepoxide (mg)	Diazepam (mg – range)	Lorazepam (mg – range)
Day 1	200 (max: 250)	40 – 160 (max: 50 – 200)	8 – 32 (max: 10 – 40)
Day 2	160	32 – 128	2 – 8
Day 3	120 – 130	24 – 104	4,8 – 21
Day 4	100	20 – 80	4 – 16
Day 5	80	16 – 64	3,2 – 13
Day 6	60	12 – 48	2,4 – 10
Day 7	40	8 – 32	1,6 – 6
Day 8	30	6 – 24	1,2 – 4,8
Day 9	20	4 – 16	0,75 – 3,2
Day 10	10	2 – 8	0,5 – 1,6

BZD: benzodiazepines; DT: delirium tremens; Chlordiazepoxide: long duration (5 – 30 hrs); Diazepam: long duration (variable); Lorazepam: intermediate duration(6 – 8 hrs);

Adapted from: The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015

Opioid dependence

- Methadone treatment requires specialist intervention – the use of methadone is readily fatal, opioid withdrawal is not;
  - Higher doses of methadone (60 to 100 mg/day) more effective than lower dosages;
  - If opioid and cocaine dependence → methadone or buprenorphine can lead to ↓ cocaine use;
- Suboxone (buprenorphine + naloxone) → if risk of diversion and injecting of buprenorphine;
- Naltrexone in relapse prevention: inconclusive evidence and high risk of fatal overdose;

↓ or prevent withdrawal

Table 6.7 Choosing between buprenorphine and methadone

	Methadone	Buprenorphine
Withdrawal syndrome	Appears to be more marked – best for maintenance programmes	Appears to have a milder withdrawal syndrome than methadone and therefore may be preferred for detoxification programs[6,7]
Differences in side-effect profiles may effect patient preference	Methadone may be associated with QTc prolongation and torsade de pointes (see later in this section)	Buprenorphine is often perceived as less sedating then methadone
Effectiveness	Higher dose methadone maintenance treatment (>60 mg) appears more effective than buprenorphine. However there are no adequate trials of high dose buprenorphine (16–32 mg) compared with high dose methadone maintenance treatment[10]	Buprenorphine is less effective than methadone at retaining patients in treatment at the guidance dose ranges
Combining with other medications	Methadone levels may alter with drugs that inhibit/induce CYP3A4 such as erythromycin, several SSRIs, ribavirin and some anticonvulsants and HIV medications. This may make dose assessment difficult, if a person is not consistent in their use of these CYP3A4 inhibiting drugs	Buprenorphine is less affected by drug interactions and may be preferable for some patients

Faggiano et al., 2003; National Institute for Health and Clinical Excellence, 2007; Minozzi et al., 201

Adapted from: The Maudsley Prescribing Guidelines in Psychiatry 12th edition, 2015

Stimulants dependence (cocaine and amphetamines)

- Withdrawal and substitution treatment → without evidence-based pharmacological treatments;
- Withdrawal → symptomatic relief (hypnotics and anxiolytics);
- Maintenance treatment:
  - Lamotrigine has been considered for cocaine;
  - Naltrexone and mirtazapine may be beneficial for cocaine and amphetamine use;
  - *A recent systematic review of dexamphetamine, bupropion, methylphenidate and modafinil as replacement therapies found no reduction in amphetamine use or craving and no increase in sustained abstinence* … but in patients that have been prescribed dexamphetamine → gradually detoxified over several months *or* continue (if … worse consequences);

Srisurapanont et al., 2001; de Lima et al., 2002; Rounsaville et al., 2004; Department of Health. Drug misuse and dependence. UK guidelines on clinical management , 2007; National Institute for Health and Clinical Excellence, 2007; Dutra et al, 2008; Haile et al, 2013; Perez-Mana et al., 2013;

GBL and GHB dependence

- Withdrawal (agitated delirium):
  - Early withdrawal symptoms → diazepam, 20 mg → repeat at 2 hourly intervals until symptoms are controlled (≈ 60–80 mg/1st 24 hours);
  - Baclofen 10–20 mg every 8 hours → continue for 3 days;

GBL (γ-butaryl-lactone, a pro-drug of GHB) and GHB (γ-hydroxybutyrate

Bell et al. 2011; Zvosec et al., 2011;