Psychopharmacological treatment of first episode psychosis

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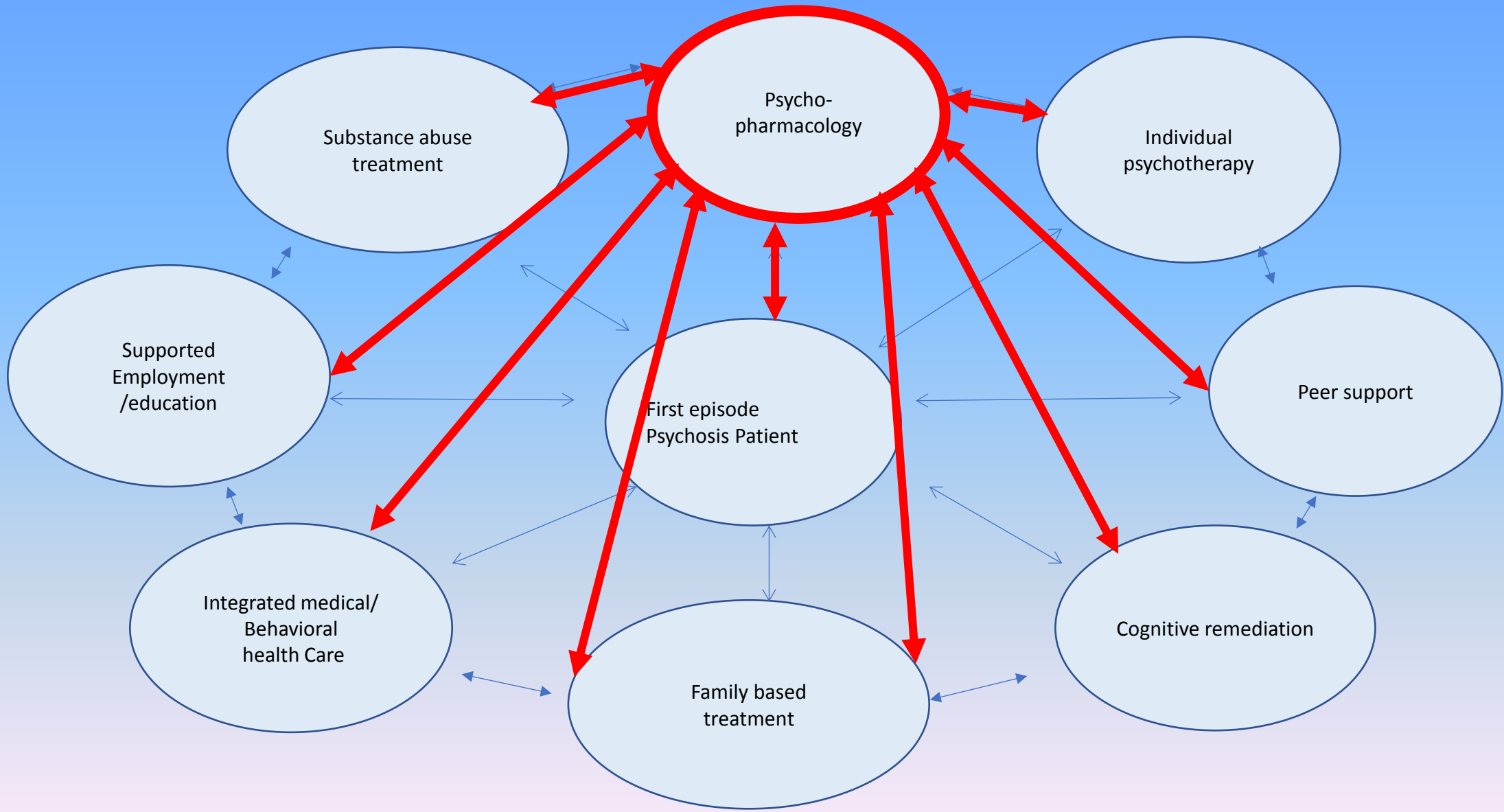
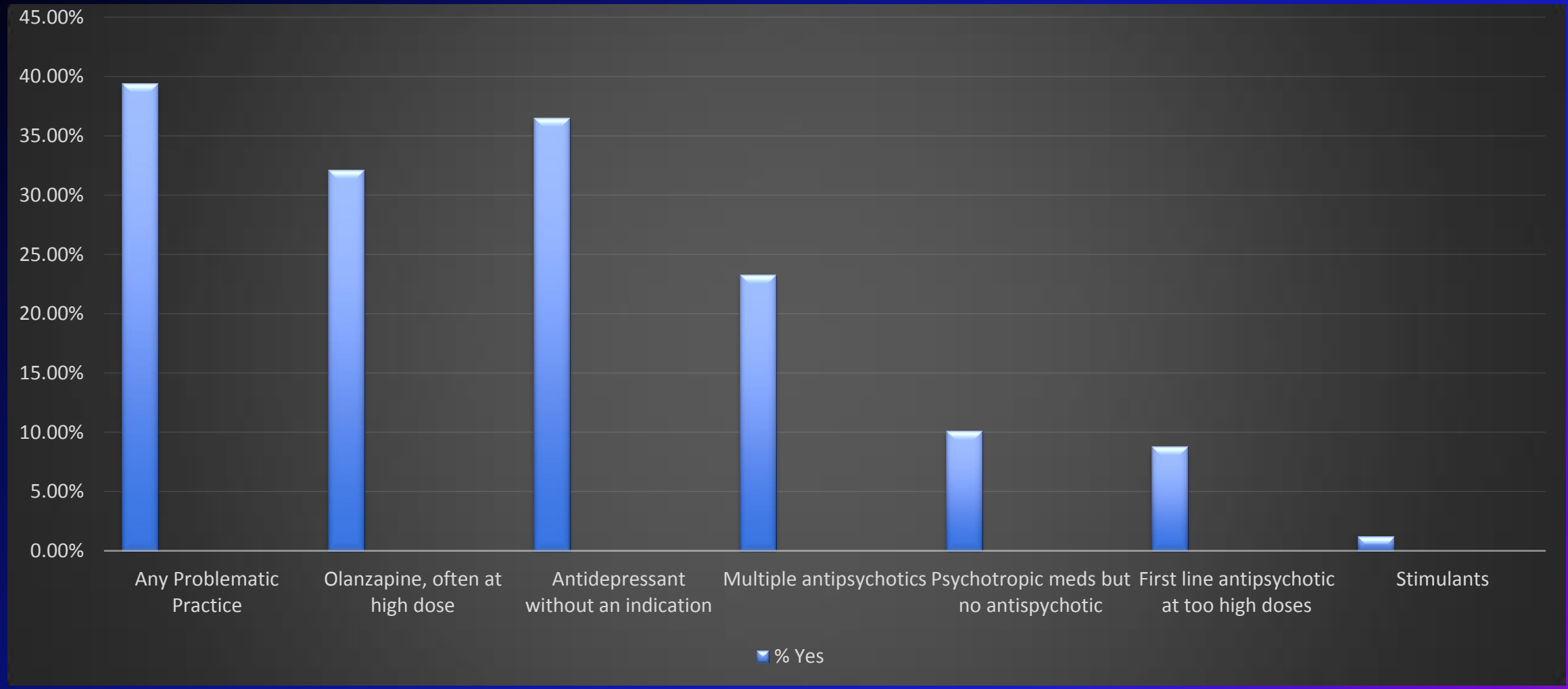


Prescribing practices in management of early course psychotic disorders

39.4% of Patients Received Problematic Psychotropic Medications at Entry Into the RAISE-ETP Study



Some patients received more than one problematic prescription

Robinson et al. American Journal of Psychiatry, 2015

The seven commandments of good prescribing.

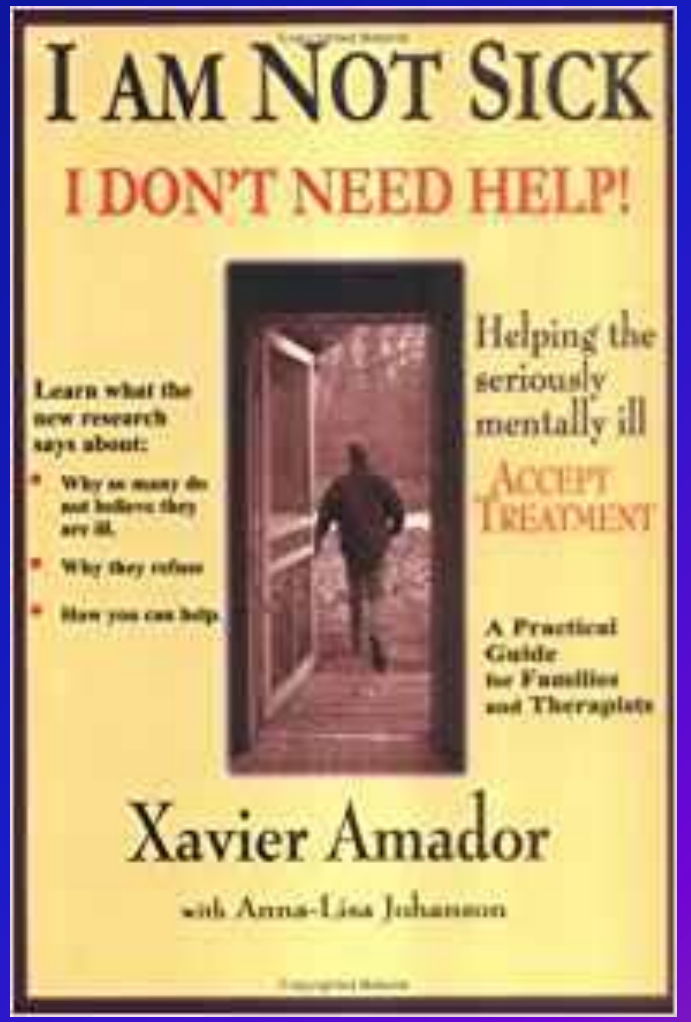
- Connecting and consent.
- Comprehensive assessment.
- Correct choice of medications.
- Correct dose and duration.
- Compliance.
- Collaborative decision making
- Comorbidity.

1. Connecting and engaging with the patient.

- Use terms that patient can understand “psychosis” rather than “schizophrenia” initially
- Tailor education to individual’s illness stage and ability to process
- Involve family members early; have them as part of your team and set up open communication
- Correct mis-information (e.g. that it is a split-mind disorder, that it is incurable, etc)
- Teach pathophysiology (e.g. dopamine imbalance) as connected to treatments (e.g. antipsychotic medications)
- Emphasize risk- liability models (e.g. asthma, high blood pressure)
- Some repetition is good; emphasize interaction

The LEAP principle

Listen
Empathize
Agree
Partner



The Role of the Therapeutic Alliance in the Treatment of Schizophrenia Relationship to Course and Outcome Arlene F. Frank, PhD; John G. Gunderson, MD *Arch Gen Psychiatry.* 1990;47(3):228-236

2. Comprehensive assessment

- Comprehensive history and examination to arrive at an accurate diagnosis , and assess/rule out antecedent/ comorbid medical illness including metabolic status
- Get all possible records, but often the patient is the only source of vital information. Complete assessment may take months
- Involve family and other care-givers, assess patient and family attitudes to medications
- Inquire about prior treatment response, and side effects
- Clarify compliance: medication taken versus medication prescribed during prior treatment - they often/usually are different.
- Inquire about the use of over-the-counter or “alternative” medicines
- Obtain and review appropriate lab results as needed (e.g. liver and kidney function; glucose and lipid profile

3. Choosing the right treatment.

- Aim for overall remission, not just symptom improvement
- Choose an antipsychotic with a favorable side effect profile and give for up to 4 months, either as an oral or a long acting formulation
- Use doses around half of what is used with multi-episode schizophrenia
- Monitor side effects closely— first episode patients are also more sensitive to side effects
- Monitor closely for medical co-morbidities
- Use the patient self ratings and your ratings to get all the information needed to make the best decisions within a shared decision making process

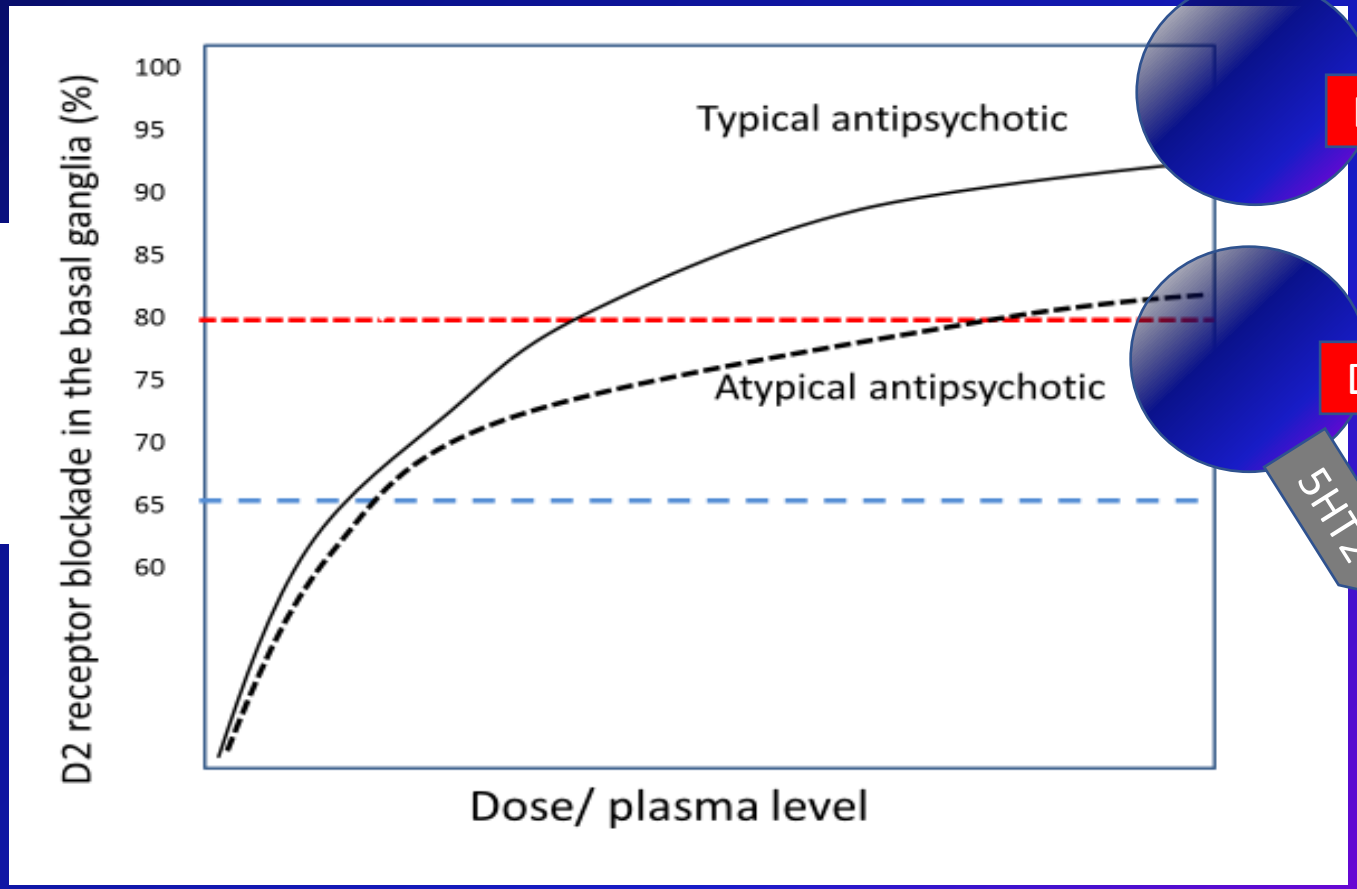
Adapted from: Delbert Robinson MD

Are Second generation antipsychotics better?

Int J Neuropsychopharmacol. 2013 July ; 16(6): 1205–1218. doi:10.1017/S1461145712001277.

Efficacy and Safety of Individual Second-Generation vs First-Generation Antipsychotics in First Episode Psychosis: A Systematic Review and Meta-analysis

Jian-Ping Zhang, MD, PhD[1], Juan A. Gallego, MD[1,2], Delbert G. Robinson, MD[1,3,4], Anil K. Malhotra, MD[1,2,3,4], John M. Kane, MD[1,2,3,4], and Christoph U. Correll, MD[1,2,3,4]



sponsored studies favored SGAs more than federally funded studies. To summarize, in FES, olanzapine, amisulpride and, less so, risperidone and quetiapine showed superior efficacy, greater treatment persistence and less EPS than FGAs. However, weight increase with olanzapine, risperidone and clozapine and metabolic changes with olanzapine were greater. Additional FES studies including broader-based SGAs and FGAs are needed.

Advantages and disadvantages of APDs

	ADVANTAGES	DISADVANTAGES
Typical APDs **(e.g., haloperidol, fluphenazine, thiothixene)**	Effective with positive symptoms Relatively low risk of weight gain/ metabolic syndrome Haloperidol useful in delirium, pregnancy	**Extrapyramidal syndromes (EPS)** **Prolactin elevation**
Atypical APDs **(aripiprazole, clozapine, olanzapine, quetiapine, risperidone , ziprasidone, Lurasidone)**	**Effective with positive symptoms,** **Relatively low EPS potential[1]** **Relatively less prolactin elevation[2]**	**Weight gain[3]** **Increased risk of metabolic syndrome (though not all atypical APDs)** **Expensive**

Medications to Try First

- Guidelines differ but there is general agreement that olanzapine and clozapine should not be first line agents due to their side effect profiles
- In RAISE-ETP, it is recommended that chlorpromazine and haloperidol should be second line agents due to side effects and, for haloperidol, questions about maintenance efficacy
- RAISE-ETP first line agents are the remaining medications with relevant data: aripiprazole, quetiapine, risperidone, ziprasidone
- Paliperidone does not have first episode dosing data but is closely related to risperidone

Courtesy: Delbert Robinson MD

Conventional and Atypicals clearly differ in side effects

	HAL	ZIP	ARI	ASE	ILP	LUR	RIS	PAL	QTP	CLZ	OLZ
EPS	++	±	±	±	±	±	+	+	0	0	±
TD	++	±	±	±	±	±	±	±	±	0	±
Anticholinergic	±	±	±	±	±	±	±	±	+	++	+
Hypotension	±	±	±	±	±	±	+	+	+	++	±
Sedation	±	±	±	+	±	±	+	+	++	++	++
Weight gain	±	±	±	±	±	±	+	+	+	++	++

Key: 0 = absent; ± = mild; + = moderate; ++ = severe

Antipsychotic effect

Anti-anxiety effect

Anti-EPS

Wt gain

Orthostasis

Sleep

Cognition

TABLE 2

RELATIVE BINDING AFFINITY OF SELECTED, NEWER ANTIPSYCHOTICS FOR SPECIFIC HUMAN NEURORECEPTORS*[40,41]

Drug	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α_1	H_1	M_1
Aripiprazole[40]	1†	5	10	44	167	180	>1,000
Asenapine	7	56	3	1	4	34	>10,000
Clozapine	81	61	1	2	3	1	4
Haloperidol	1	692	23	1,000	7	100	>1,000
Iloperidone	17	165	1	70	2	62	>10,000
Olanzapine	222	>1,000	17	11	488	1	400
Paliperidone	2.3	400	1	40	8	3	>1,000
Quetiapine	95	37	4	432	1	2	173
Risperidone	25	>1,000	1	213	18	35	>10,000
Ziprasidone	22	16	1	8	22	38	>1,000

* Relative binding affinity = binding affinity in relationship to the drug's highest affinity site (ie, Ki for each site divided by the Ki for drug's highest affinity site). Hence, its relative binding affinity for its highest affinity site in the above table is 1 and for all other sites is a multiple of one as determined by this mathematical manipulation. For each drug in this table, its highest affinity and its affinity expressed in nanomolar concentration is as follows: aripiprazole, D_2 (0.34); asenapine, 5-HT_{2C} (0.27); clozapine, 5-HT_{2A} (2.59); haloperidol, D_2 (2.6); iloperidone, 5-HT_{2A} (0.20); olanzapine, H_1 (0.087); quetiapine, α_1 (8.1); paliperidone, 5-HT_{2A} (1.21); risperidone, 5-HT_{2A} (0.15); ziprasidone, 5HT_{2A} (0.12).

† Partial agonist at the D_2 receptor whereas the other drugs in this table are full antagonists.
D=dopamine, 5-HT=5-hydroxytrytophan or serotonin; α_1=alpha-1 adrenergic; H=histamine; M=muscarine.

Preskorn SH, Flockhart D. *Primary Psychiatry.* Vol 16, No 12. 2009.

4. Correct duration and dose of medication trials

- First episode patients may respond to long mono-therapy trials of antipsychotics
- Antipsychotics doses that are at 50-60% of what is used in more chronic patients are often sufficient to obtain a treatment response. Higher doses often are associated with a greater side effect burden
- The Preventing Morbidity study treated first episode patients with olanzapine or risperidone for 16 weeks
- Cumulative response rates increased steadily every study week until the end of trial
- The cumulative response rate was 40% by week 8; 54% by week 12 and 65% by week 16

J Clin Psychiatry. 2011 December ; 72(12): 1691–1696. doi:10.4088/JCP.10m06349.

Time to treatment response in first episode schizophrenia: should acute treatment trials last several months?

Juan A. Gallego, MD[a], Delbert G. Robinson, MD[a,b,c], Serge M. Sevy, MD[a,c], Barbara Napolitano, MA[d], Joanne McCormack, LCSW[a], Martin L. Lesser, Ph.D[b,c,e], and John M. Kane, MD[a,b,c]

Courtesy: Delbert Robinson MD

Response of the Initial Episode

Study	N	Drug	Response rate
Emsley et al 1999	183	Risperidone (6.1mg/day)	63% by 6 weeks
		Haloperidol (5.6mg/day)	56%
Lieberman et al 2003	263	Olanzapine (9.1 mg/day)	55% by 12 weeks
		Haloperidol (4.4 mg/day)	46%
Lieberman et al 2003	160	Clozapine (400 mg/day)	81% by 52 weeks
		Chlorpromazine (600 mg/day)	79%
Schooler et al 2005	555	Risperidone (3.3 mg/day)	75% by 12 weeks
		Haloperidol (2.9 mg/day)	78%
Robinson et al 2006	112	Olanzapine (11.8 mg/day)	44% by 16 weeks
		Risperidone (3.9 mg/day)	54%
Robinson et al 2015	198	Aripiprazole (14.8 mg/day)	63% by 12 weeks
		Risperidone (3.2 mg/day)	57%

Courtesy: Delbert Robinson MD

5. Enhancing compliance with treatment.

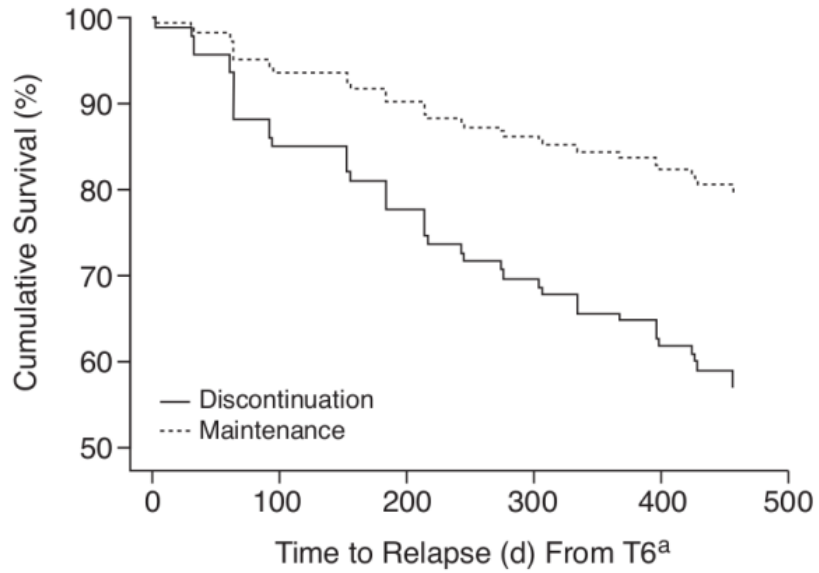
Guided Discontinuation Versus Maintenance Treatment in Remitted First-Episode Psychosis: Relapse Rates and Functional Outcome

Lex Wunderink, M.D., Ph.D.; Fokko J. Nienhuis, M.A.; Sjoerd Sytema, Ph.D.; Cees J. Slooff, M.D., Ph.D.; Rikus Knegtering, M.D., Ph.D.; and Durk Wiersma, Ph.D.

J Clin Psychiatry 2007

Results: Twice as many relapses occurred with the discontinuation strategy (43% vs. 21%, p = .011). Of patients who received the strategy, approximately 20% were successfully discontinued. Recurrent symptoms caused another approximately 30% to restart antipsychotic treatment, while in the remaining patients discontinuation was not feasible at all. There were no advantages of the discontinuation strategy regarding functional outcome.

Figure 2. Relapse Rates for the Discontinuation Strategy vs. Maintenance Treatment (survival function)

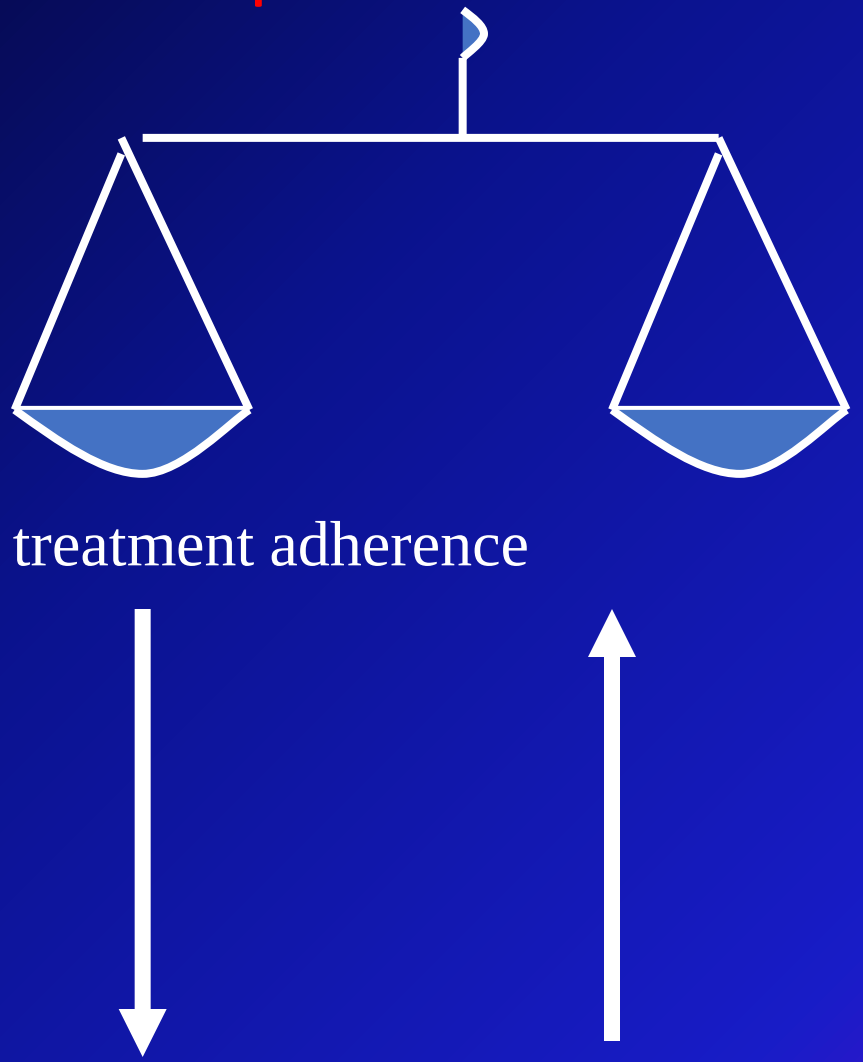


[a]T6 = start of trial (6 months after first treatment response).

- Antipsychotic discontinuation during the first years of illness is associated with increased relapse risk (Wunderink et al 2007)
- A small number of patients do not relapse after antipsychotic discontinuation , but we do not know how to predict relapse
- Using minimum effective doses is associated with better long term outcome at 7 years (Wunderink et al 2013)
- Best strategy now is to prescribe continuous antipsychotic maintenance treatment using the lowest effective doses

Causes of non-compliance.

Treatment:
lack of Efficacy
side effects
Complex regime
Costly
Poor therapeutic alliance
Person:
Cultural barriers
family prejudice
Poor Insight
Stigma
Illness
Asymptomatic
Psychosis
grandiosity
Cognitive impairment



Treatment:
Efficacy
Safety
Simplicity
Inexpensive
Good Dr Patient relationship
level of supervision
Person:
Insight
family support
Intelligence
Illness
Acceptance
Perception of severity
Perception of susceptibility

(Perkins J Clin Psychiatry, 1999)

Dialogue 1: Introducing a Long-active antipsychotic

- Patients: re-potential benefits, e.g. No hassle remembering to take meds, lower dose overall.
- Family: day-to-day contention of taking meds off the table.
- Clinician/ family: Non-compliance detected as soon as first injection missed.

Dialogue 2: When can I go off the medication, Doctor?

- Explore reasons for the wanting discontinue meds.
- Review with patient risks of Med D/C vs. benefits.
- Involve family in the discussion whenever possible.
- Reduce dose, if indicated/or switch to a more acceptable alternative.
- Develop contract with patient for continued treatment for a specified period, and periodically revisit this.
- If patient insists, consider very gradual discontinuation
- Educate re early warning signs of relapse, rescue medication, contingency plans, and regular monitoring.
- Maintain therapeutic relationship at all times!

The Risk for Psychotic Relapse is High

Year*	Relapse rate (%)	95% limit (%)		Patients still at risk at end of year
		Lower	Upper	
1	16.2	8.9	23.4	80
2	53.7	43.4	64.0	39
3	63.1	52.7	73.4	22
4	74.7	64.2	85.2	9
5	81.9	70.6	93.2	4

n=104 first-episode schizophrenia patients
*Year(s) since previous episode

Robinson D, et al. Arch Gen Psychiatry 1999;56:241–7

Approaches to enhance adherence

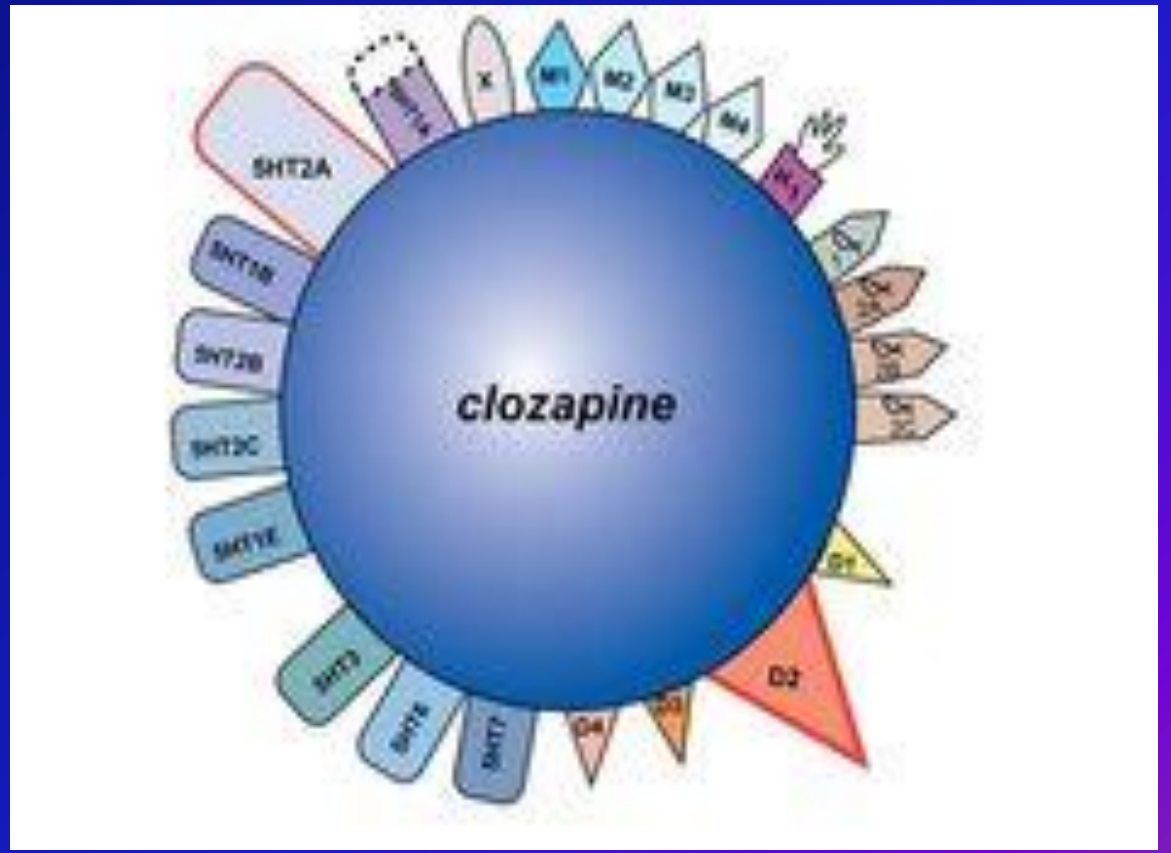
• Patient who refuses meds	• Improve therapeutic alliance; rapid acting meds; involuntary meds as last resort • Dosage adjustment; consider medication switch, clozapine
• Patient non-adherent because meds not working	
• Patient non-adherent because of side effects	• Dosage adjustment; consider medication switch; monitor & educate re. Side effects
• Patient does not show up for first appointment	• Improve hospital to clinic continuity; make care more accessible and patient friendly
• Patient who frequently misses/forgets meds/appts	• Cues to remember; memory aids such as pillboxes and alarm watches; phone call reminders; Long acting APDs • Compliance therapy; continuing psychoeducation; cognitive remediation
• Patient who believes he/she does not need meds	

6. Collaborative (Shared) decision making

- Find an aspect of the patient's illness that they agree is a problem as an entry point to explore the extent of symptoms. This could be: A symptom that the patient experiences as negative (usually this is anxiety or worry, sometimes depression), Problems with role function, or Problems with social functioning
- If evidence-based treatment is not agreed upon, we continue to work with them with the hope that with more education they will accept evidence based treatment
- Make shared medication choices within the evidence base.
    - If a group of medications have equivalent effectiveness evidence, choice within that group is based upon patient preferences (e.g. What side effect can you tolerate?)

Managing treatment resistance: Clozapine

- Rule out covert non-adherence, under-treatment and medical illness. Consider revising diagnosis
- Consider clozapine in patients who have persistent positive symptoms after trials of two antipsychotics and should be the treatment
- Consider clozapine at earlier treatment stages for patents with persistent suicidal ideation
- There are no data on clozapine available specific for first episode patients with persistent positive symptoms



Dialogue 3: Introducing Clozapine

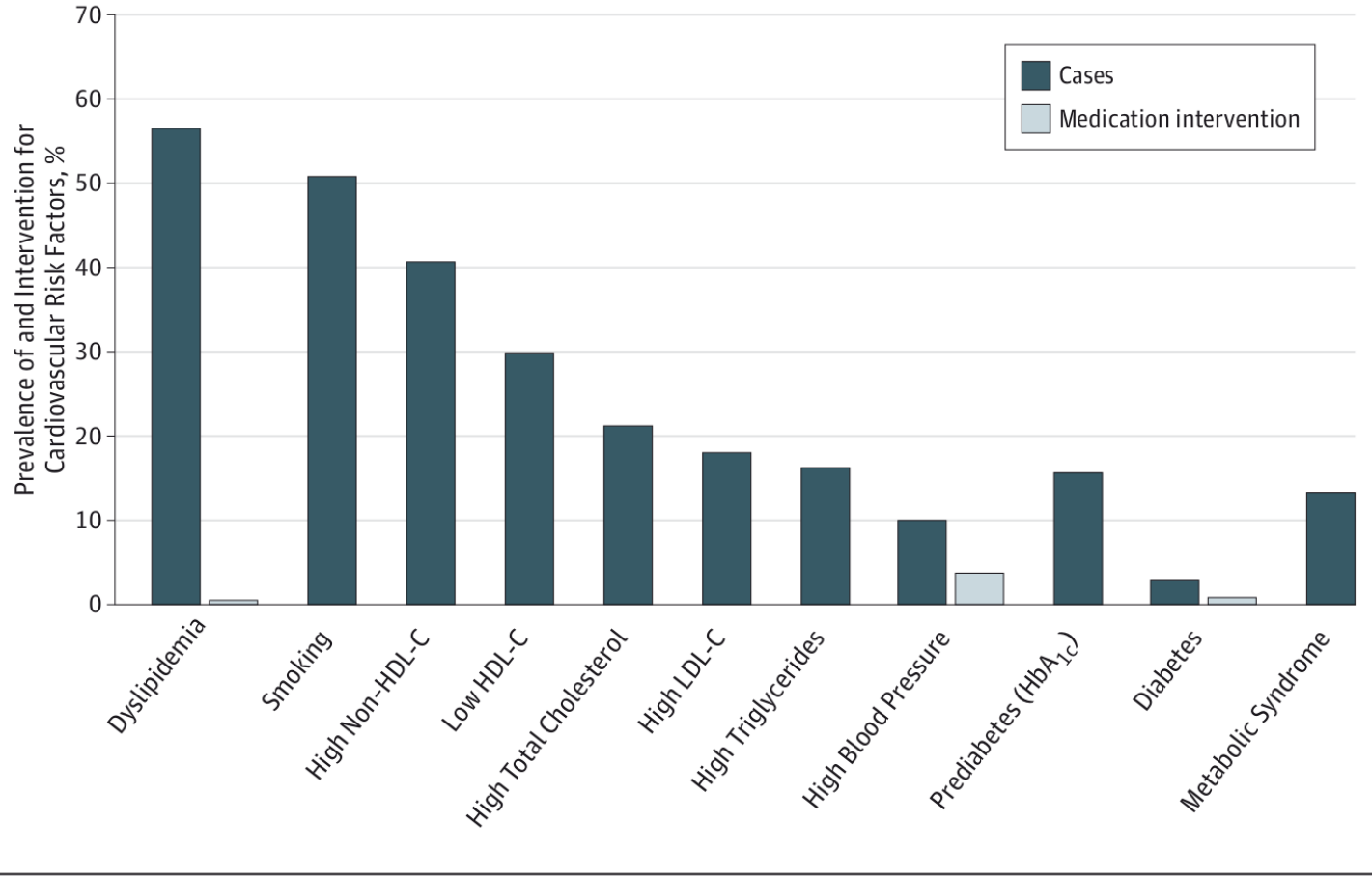
- Effective for treatment resistant positive symptoms.
- Freedom from irreversible side effects such as TD.
- Potential benefits for suicide prevention.
- Potential benefits of reducing substance craving.
- Side effects are a significant concern, but can be reduced with regular monitoring.
- Regular monitoring with blood tests can be a hassle, but can give the framework for frequent psychotherapeutic visits.

Managing side effects

- Prevent side effects by careful history, and appropriate choice
- Early monitoring, and psychoeducation
- “start low- go slow” strategy
- Reduce dose if possible
- Consider switching antipsychotics versus adding side effect medications

7. Co-Morbidities Are Common in FEP

Figure 2. Prevalence of Smoking, Lipid Abnormalities, Hypertension, Diabetes, and Metabolic Syndrome and Respective Medication Treatment for the Conditions



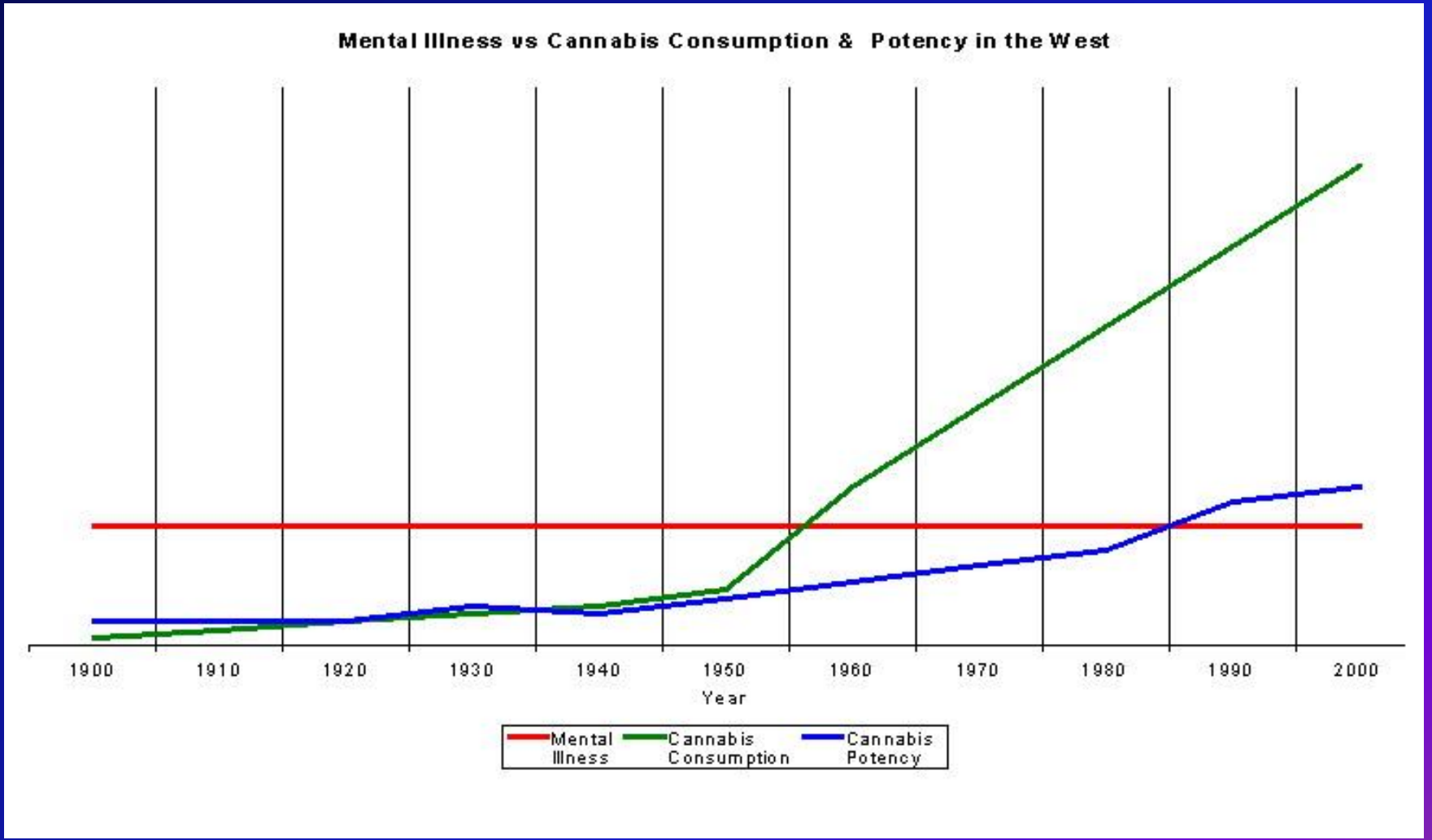
Correll et al JAMA Psychiatry 2014

Depressive Symptoms are also common

- Depressive symptoms are common with a first episode of schizophrenia.
- Rule out “pseudo-depression (i.e. negative symptoms, parkinson side effects). Consider bipolar disorder
- Depressive symptoms may be a core part of the acute illness. These symptoms usually resolve with antipsychotic monotherapy as the psychosis remits (see Koreen et al; Am J Psychiatry 1993; 150:1643-1648)
- Guidelines for when to initiate adjunctive antidepressant treatment with first episode patients are not available
- Since most depressive symptoms will remit with antipsychotic treatment alone, prescription of adjunctive antidepressants for all first episode patients with depressive symptoms is not warranted
- Given what is known about antipsychotic treatment with first episode patients (effective dose ranges are low in comparison with those for multi-episode patients; marked side effect sensitivity), consideration of using slow titration and low to moderate antidepressant doses is reasonable in the absence of data

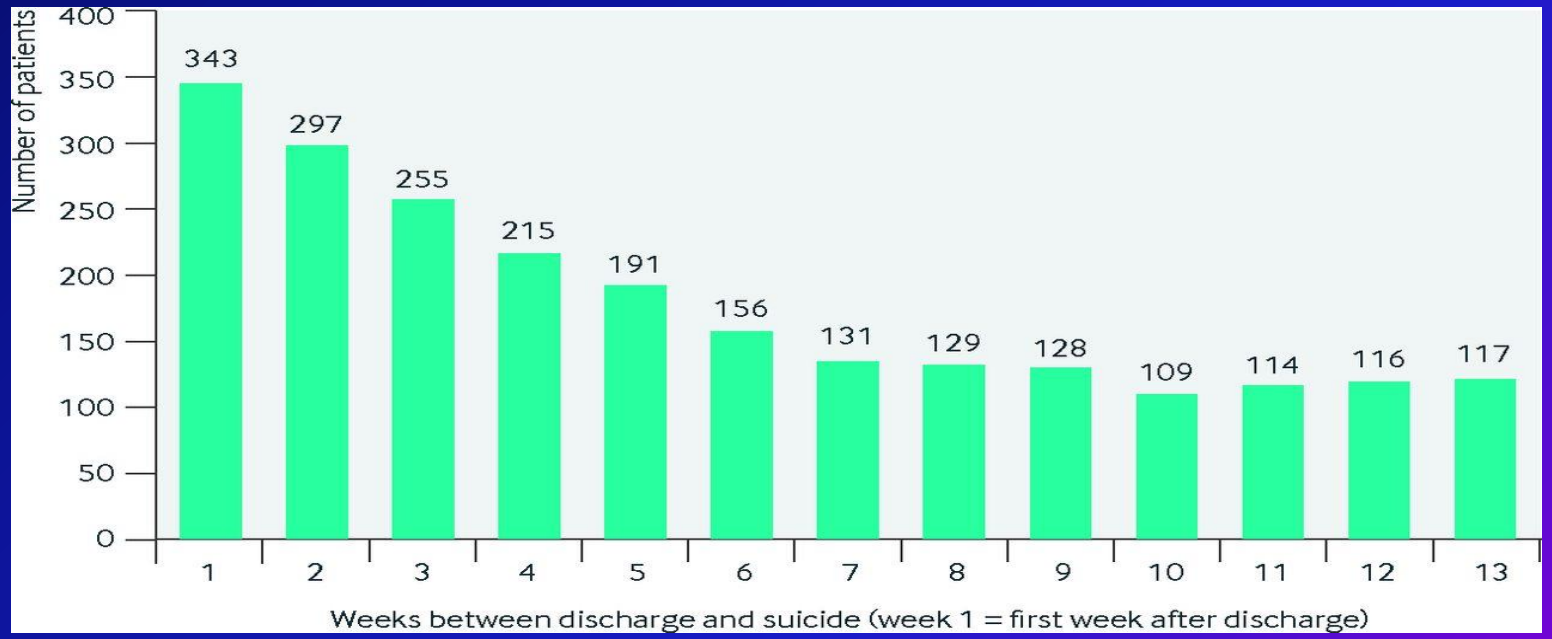
Assessing substance abuse comorbidity

- Cannabis and alcohol are the most prevalent substances of abuse.
- Cannabis consumption and potency have seen is dramatic increase in the US in recent years
- It is often difficult to distinguish substance induced psychosis from schizophrenia with substance use
- Clinicians sometimes automatically assume that young patients who present with psychosis and substance use have a drug induced psychosis.
- An important clinical point is to get a chronology of the psychotic symptoms and of the substance use…Look for periods of psychosis in the absence of substance use



Suicide Assessment and Prevention

- The first years of schizophrenia mark the time of greatest risk for suicide attempts
- The weeks after discharge are a period of increased risk
- Make sure to look for signs of hopelessness, resignation, or ruminations about falling behind peers or own family expectations
- Make sure to inquire about suicidal thinking or behaviors; family members can be a good source of information
- Psychotherapy is critically important; clozapine is worth considering



James M Bolton et al. BMJ 2015;351:bmj.h4978

Summary: Pharmacological management of first episode psychosis: what we know and what we don't know

- **Stabilization**
- ▸ Which antipsychotic medications to begin with?
- ▸ What is the recommended dose of APD?
- ▸ What is the duration of an initial trial of an APD?
- ▸ Which APD should be considered when the initial antipsychotic fails?
- ▸ How long should a second antipsychotic trial last?
- ▸ When to consider long-acting injectable APDs?
- ▸ When are combinations of APDs appropriate?
- **Maintenance of remission**
- ▸ Which APD for maintenance of remission ?
- ▸ What is the dose of maintenance APD?
- ▸ What is the duration of maintenance treatment following a first episode?
- ▸ Is targeted intermittent APD treatment advisable?
- **Treatment resistance**
- ▸ When should clozapine be considered in first first-episode psychosis?
- ▸ What is the recommended dose of clozapine?
- ▸ How long on clozapine to assess response?
- ▸ What to do when clozapine fails? ?

- **Stabilization**
- ▸ Atypical preferred; avoid olanzapine or clozapine as first choice
- ▸ Lower doses (~50-60% of standard dose for multi-episode patients)
- ▸ At least 16 weeks
- ▸ Consider side effects; use shared decision making
- ▸ No clear guideline
- ▸ No clear guideline
- ▸ Generally not advisable
- **Maintenance of remission**
- ▸ Preferably the APD found to be effective
- ▸ Minimum effective dose
- ▸ No clear guideline
- ▸ Not advisable
- **Treatment resistance**
- After failure of at least two antipsychotics in adequate trials
- ▸No clear guideline
- ▸ No clear guideline
- ▸ No clear guideline

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