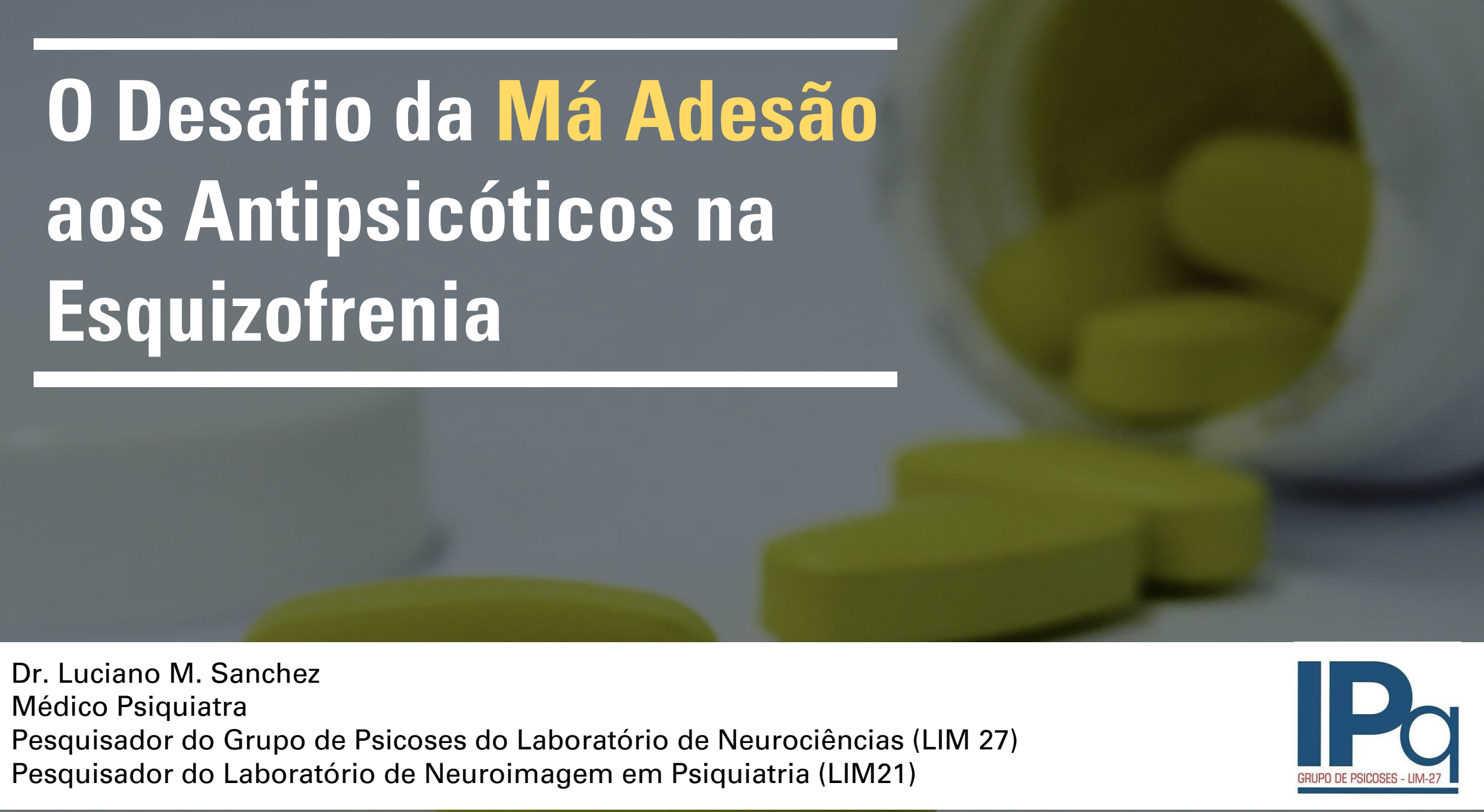


O Desafio da Má Adesão aos Antipsicóticos na Esquizofrenia

Dr. Luciano M. Sanchez
Médico Psiquiatra
Pesquisador do Grupo de Psicoses do Laboratório de Neurociências (LIM 27)
Pesquisador do Laboratório de Neuroimagem em Psiquiatria (LIM21)

GRUPO DE PSICOSES - LIM-27

SEM CONFLITOS DE INTERESSE

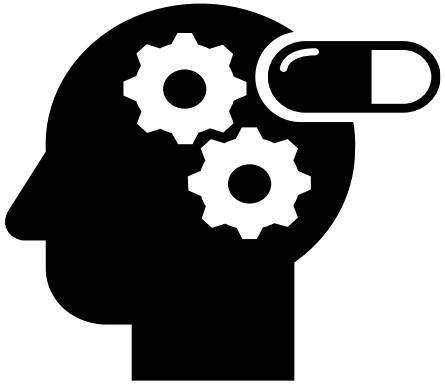
50%

dos pacientes não tomam as medicações como prescritas

1 Entendendo o fenômeno da má adesão

2 Abordagens não farmacológicas para má adesão

3 Abordagens farmacológicas para má adesão



THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—36TH YEAR. SYDNEY, SATURDAY, SEPTEMBER 3, 1949. No. 10.

LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

By JOHN F. J. CADE, M.D.,
Senior Medical Officer, Victorian Department of Mental Hygiene.

LITHIUM SALTS enjoyed their hey-day in the latter half of last century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates. It was shown that if pieces of cartilage with urate deposits were immersed in solutions of sodium, potassium and lithium carbonate, the urate was dissolved first from that piece immersed in the lithium carbonate solution.

As time went on and lithia tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects were more and more commonly seen.

Garrod (1859) wrote of lithium carbonate: "When given internally in doses of from one to four grains dissolved in water, two to three times a day, it produces no direct physiological symptom . . . their use does not appear to be attended with any injurious consequences." And

guinea-pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity. The great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt. When an aqueous solution of 8% urea, saturated with lithium urate, was injected, the toxicity was far less than was expected. It looked as if the lithium ion might have been exerting a protective effect. To determine this, more observations were made, lithium carbonate being used instead of lithium urate. An 8% aqueous solution of urea kills five out of ten guinea-pigs when injected intraperitoneally in doses of 1·25 millilitres per ounce of body weight. When 0·5% lithium carbonate in an 8% urea solution was injected in the same dosage, all ten animals survived; and this argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea.

To determine whether lithium salts *per se* had any discernible effects on guinea-pigs, animals were injected intraperitoneally with large doses of 0·5% aqueous solution of lithium carbonate. A noteworthy result was that after a latent period of about two hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid.

It may seem a long distance from lethargy in guinea-pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate

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CASE I.—W.B., a male, aged fifty-one years, who had been in a state of chronic manic excitement for five years, restless, dirty, destructive, mischievous and interfering, had long been regarded as the most troublesome patient in the ward. His response was highly gratifying. From the start of treatment on March 29, 1948, with lithium citrate he steadily settled down and in three weeks was enjoying the unaccustomed surroundings of the convalescent ward. As he had been ill so long and confined to a "chronic ward", he found normal surroundings and liberty of movement strange at first. Owing to this, as well as to housing difficulties and the necessity of determining a satisfactory maintenance dose, he was kept under observation for two months. He remained perfectly well and left hospital on July 9, 1948, on indefinite leave with instructions to take a maintenance dose of lithium carbonate, five grains twice a day. The carbonate had been substituted for the citrate as he had become intolerant of the latter, complaining of severe nausea. He was soon back working happily at his old job. However, he became more lackadaisical about his medicine and finally ceased taking it. His relatives reported that he had not had any for at least six weeks prior to readmission on January 30, 1949, and was becoming steadily more irritable and erratic. He ceasedl work just before Christmas. On readmission to hospital he was at once started on lithium carbonate, ten grains three times a day, and in a fortnight had again settled down to normal. The dose of carbonate was then reduced to five grains three times a day, and in a further two weeks to five grains twice a day. He is now (February 28, 1949) ready to return to home and work.

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CASE VI.—A.M., a man of sixty years, suffered from manic-depressive insanity associated with alcoholism. His previous attacks had been mainly depressive, but he had had a manic phase lasting five months two years previously. By November 17, 1948, he had been developing a manic phase for a fortnight, steadily worsening until now he was noisy, restless and aggressive. On this date he commenced taking lithium citrate 20 grains three times a day. In a week he was settling down, but at the end of a fortnight the administration of lithium citrate had to be temporarily discontinued as he was showing toxic symptoms—he was asthenic and tremulous, with slurring speech. The toxic symptoms disappeared in four days and citrate administration was resumed with a dose of 10 grains three times a day. By this time he had settled down completely. On February 14, 1949, after lithium citrate administration had been discontinued for seven weeks, he was again becoming unsettled and losing weight. Given lithium citrate 20 grains three times a day, he once again settled down promptly in four days, and at the end of a week when he had put on three pounds in weight the dose was reduced to a maintenance dose of 10 grains once daily.

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Os pacientes tomam as medicações?

Pacientes com esquizofrenia/psicose que não aderem às medicações anti-psicóticas:

1962 44% das medicações não eram tomadas como prescritas

1986 Revisão com 3 mil pacientes
Não adesão entre 10 e 76% - 41% na média

1998 Revisão de 22 artigos, período de 20 anos e mais 3 mil pacientes
Não adesão entre 24 e 90% (58% média)

2002 Revisão de 39 artigos, período 1981 a 2002 com mais 20 mil pacientes
Não adesão entre 4 e 72% (40% média)
Com critérios mais estritos – 47% média

Grande quantidade de pacientes não aderentes

Ausência de definição padronizada para má adesão

+

Ausência de método confiável ou mesmo padronizado para medir adesão

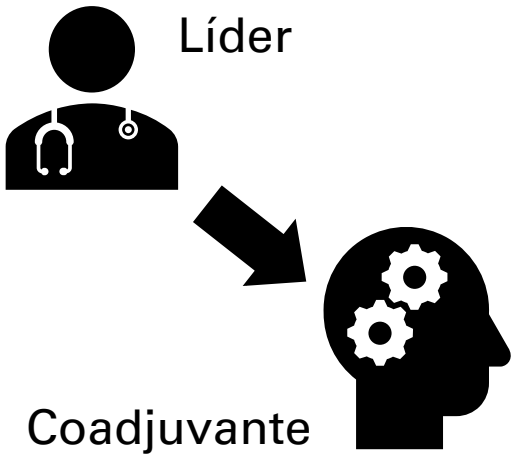
⬇

Grande variabilidade nos resultados

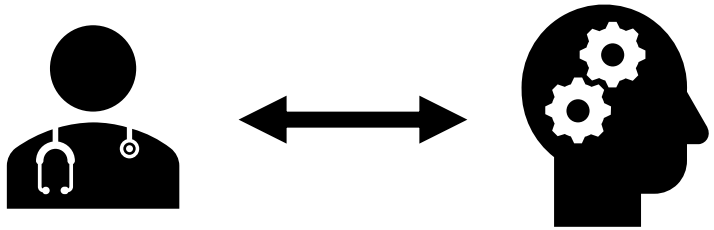
Como definir e medir má adesão?

Mudança na terminologia ao longo do tempo reflete a presença de **2 modelos distintos** de relação médico-paciente:

Conformidade (Complience)



Adesão (Adherence)

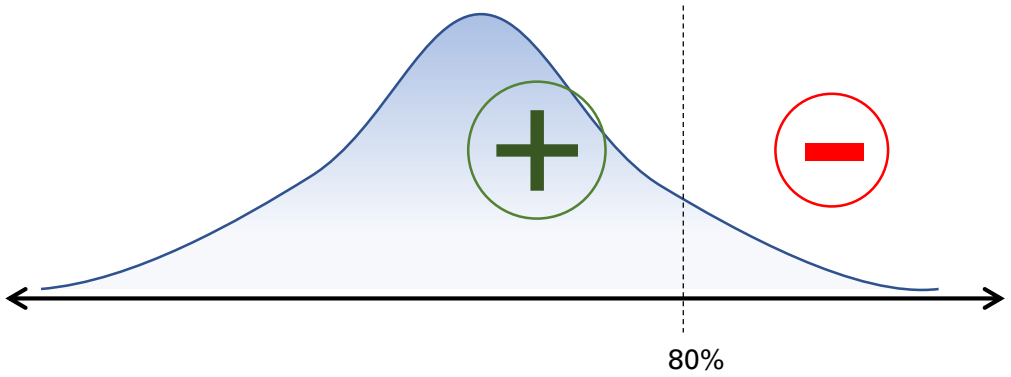


médico e paciente, ativamente, se engajam em decisões compartilhadas dentro dos seus papeis específicos

Adesão ao tratamento: Até que ponto o comportamento de uma pessoa coincide com os conselhos médicos ou de saúde

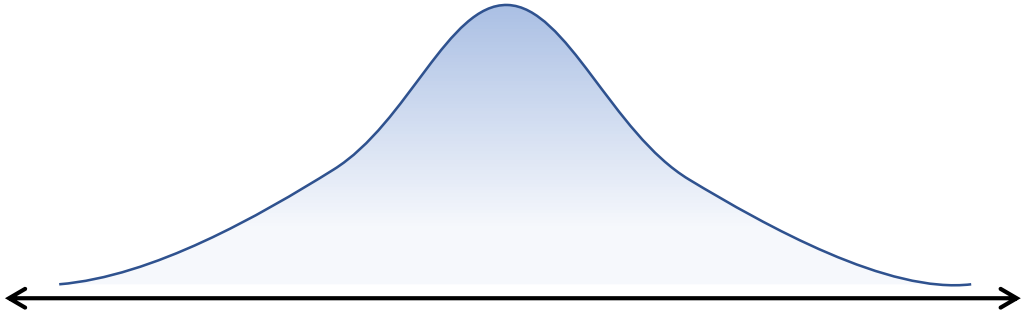
Como definir e medir má adesão?

Abordagem categórica



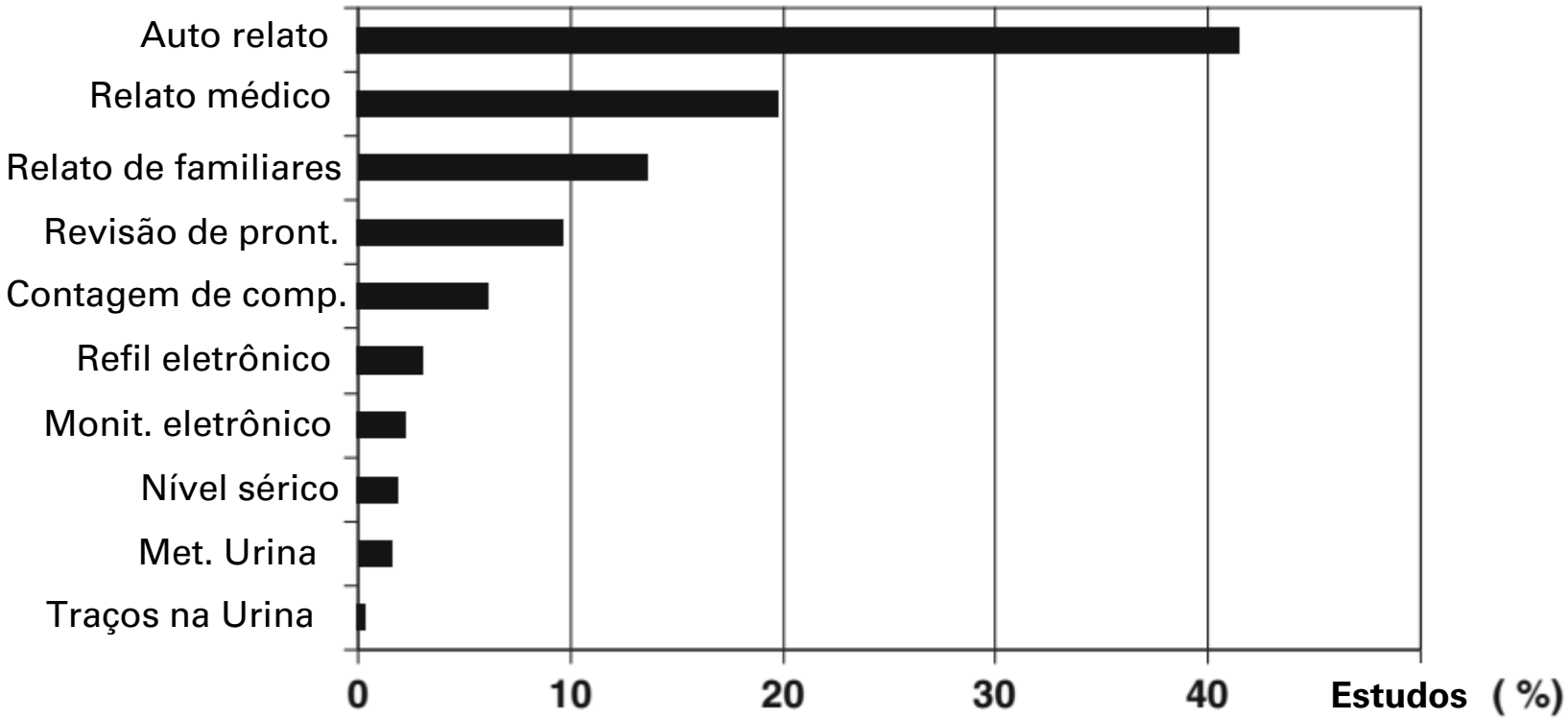
- não considera pacientes que tomam medicação em excesso
- Cut-off para pacientes serem considerados não aderentes é muito heterogênea
- Classificação de parcialmente aderente não distingue bem entre a natureza da aderência

Abordagem dimensional



- Abordagem dimensional é difícil na prática, necessita de amostras grandes e tem interpretação difícil

Como definir e medir má adesão?



Como definir e medir má adesão?

Relatos

- Existe grande variabilidade nos relatos e taxas são subestimadas
- Psiquiatras tendem a subestimar a adesão

Brief Adherence Rating Scale
Buchanan criteria
Compliance Rating Scale
Medication Adherence Questionnaire
Service Engagement Scale
Visual Analogue Scale for Assessing Treatment Adherence

Monitoramento Eletrônico

- Detecta taxas maiores de não adesão que outros métodos
- Indica apenas que o remédio está fora da embalagem
- Alta correlação com contagem de comprimidos

Nível sérico e traços na urina

- Avalia apenas a tomada nos últimos dias
- Sujeitos a variação individual e metabolismo
- Pacientes aumentam a tomada das med. antes da avaliação

A concordância entre os métodos é muito baixa e a correlação entre a maior parte deles é baixa.

Como definir e medir má adesão?

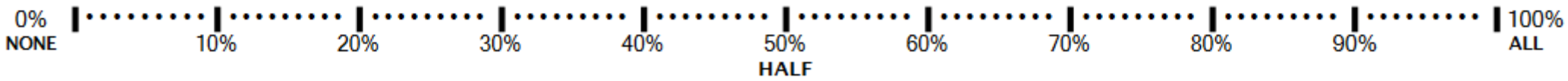
Patient Identification:_____ Date: _____

BRIEF ADHERENCE RATING SCALE

The following information is obtained by the clinician:

1. How many pills of (name of antipsychotic) did the doctor tell you to take each day?		
2. Over the month since your last visit with me, on how many days did you NOT TAKE your _____(name of antipsychotic)?	Few, if any (<7)	
	7-13	
	14-20	
	Most (>20)	
3. Over the month since your last visit with me, how many days did you TAKE LESS THAN the prescribed number of pills of your (name of antipsychotic)? **Note:** 1 = poor adherence 4 = good adherence	Always/Almost Always (76-100% of the time) = 1	
	Usually (51-75% of the time) = 2	
	Sometimes (26-50% of the time) = 3	
	Never/Almost never (0-25% of the time) = 4	

Please place a single vertical line on the dotted line below that you believe best describes, out of the prescribed antipsychotic medication (_____) doses, the proportion of doses taken by the patient in the past month.



Response struck on above line (%) = _____

Como definir e medir má adesão?

Abordagem epidemiológica - Contagem de comprimidos

Medication Possetion Ratio

$$\frac{\text{Total de refil de comp.}}{\text{Total de comp. prescritos}}$$

< 8.0 45+ mil pacientes - 40% 1 AP e 38% 2 Aps
1,5 mil pacientes - 10,2%

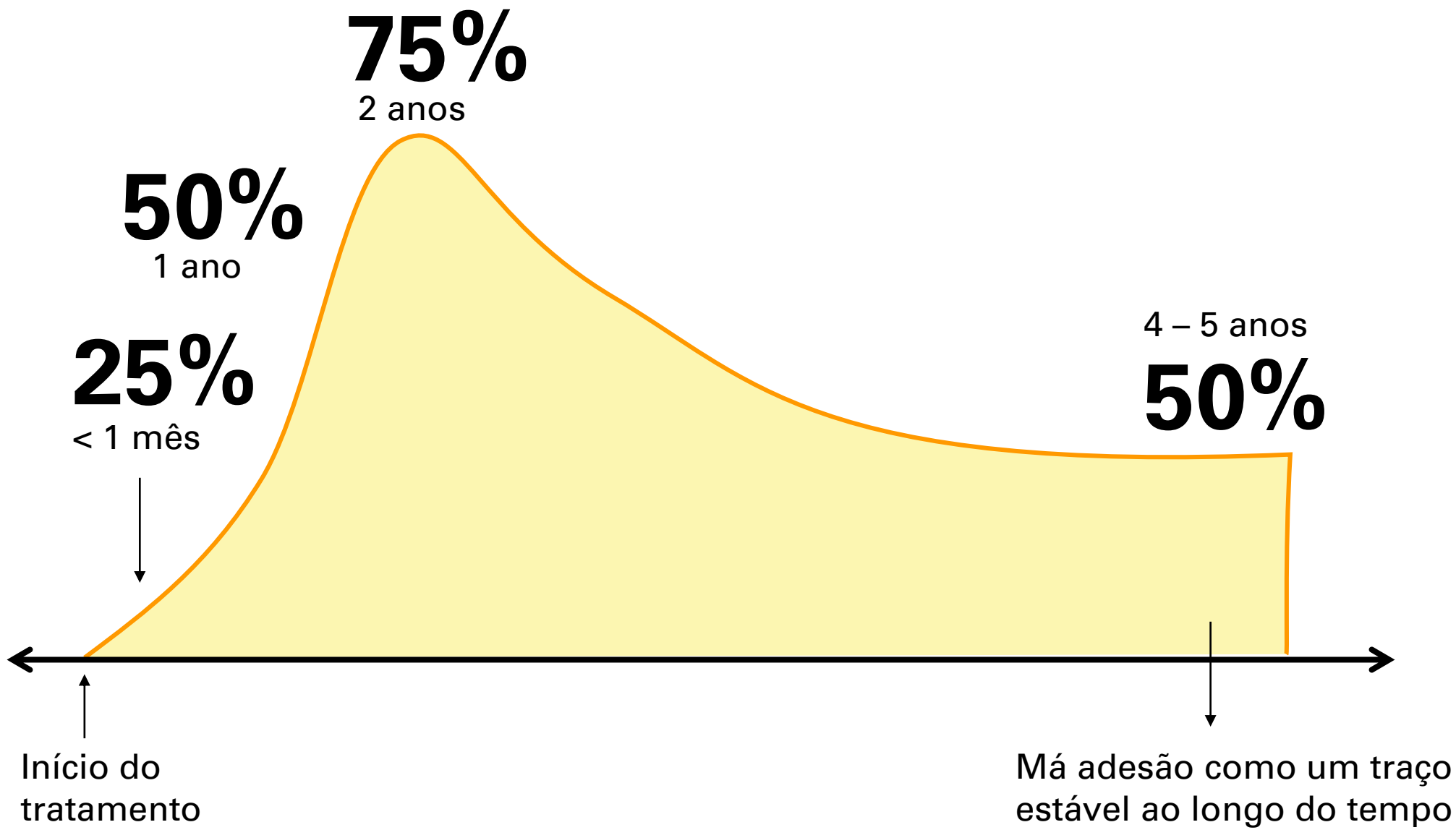
< 7.0 4,3 mil pacientes - 16%

40 - 60%

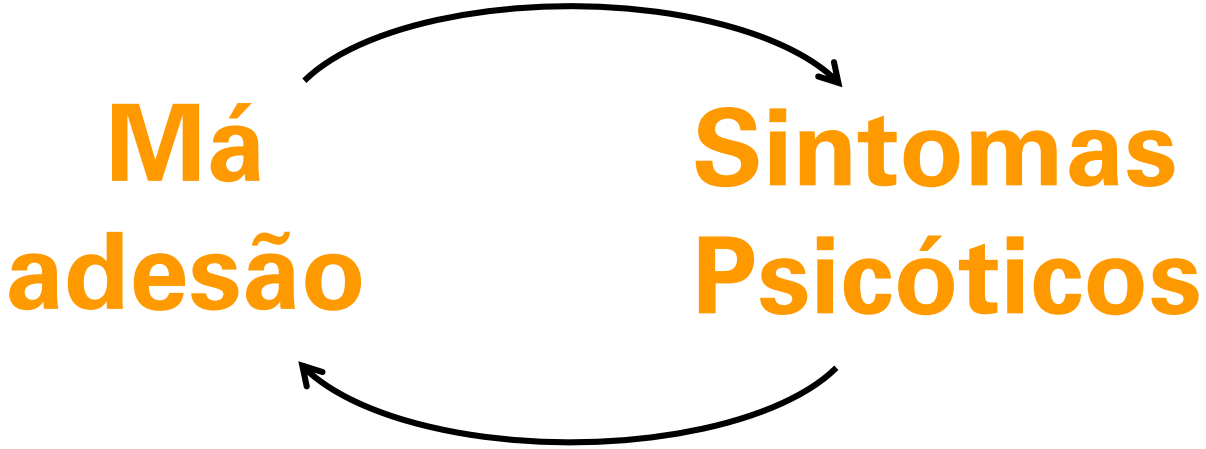
Variação entre os estudos

24 - 30%

Não comparece às consultas


75%
2 anos
50%
1 ano
25%
< 1 mês
4 – 5 anos
50%
Início do tratamento
Má adesão como um traço estável ao longo do tempo

Quais as consequências da má adesão?



Ocupação de receptores abaixo do limiar necessário

Supersensibilidade compensatória de receptores induzida pelo uso crônico de antipsicóticos

↓ 20% adesão

↑ 3.1 PANSS

Pacientes com má adesão se mantêm com sintomas mais severos, principalmente, sintomas positivos

Após 1 ano de follow-up

68% das recaídas por ineficácia neuroléptica

38% não adesão aos neurolépticos

Mesmo 2 semanas de 50 – 70% de adesão podem

↑ 5x

o risco de recaídas

Quais as consequências da má adesão?

↓ Adesão

Efeitos clínicos e comportamentais

Impacto no sistema de saúde, família, sociedade e pesquisa

↑ Impacto econômico e social

↑ Severidade dos sintomas (ppte positivos)
↓ Menor chance de atingir remissão
↑ Chance de recaída
↑ Risco de descontinuação completa do tratamento
↓ Funcionalidade diária
↑ Risco de suicídio
↑ Risco de comportamentos violentos
↑ Risco de ser vítima ou ter envolvimento com crime
↑ Mortalidade (pequeno)
↑ Risco de hospitalização (mesmo poucos dias)
Impacto negativo em clinical trials
Sobrecarga emocional nos cuidadores
Reforço do estigma
↑ Custos para o sistema de saúde, judiciário e social

Por que os pacientes não aderem ?

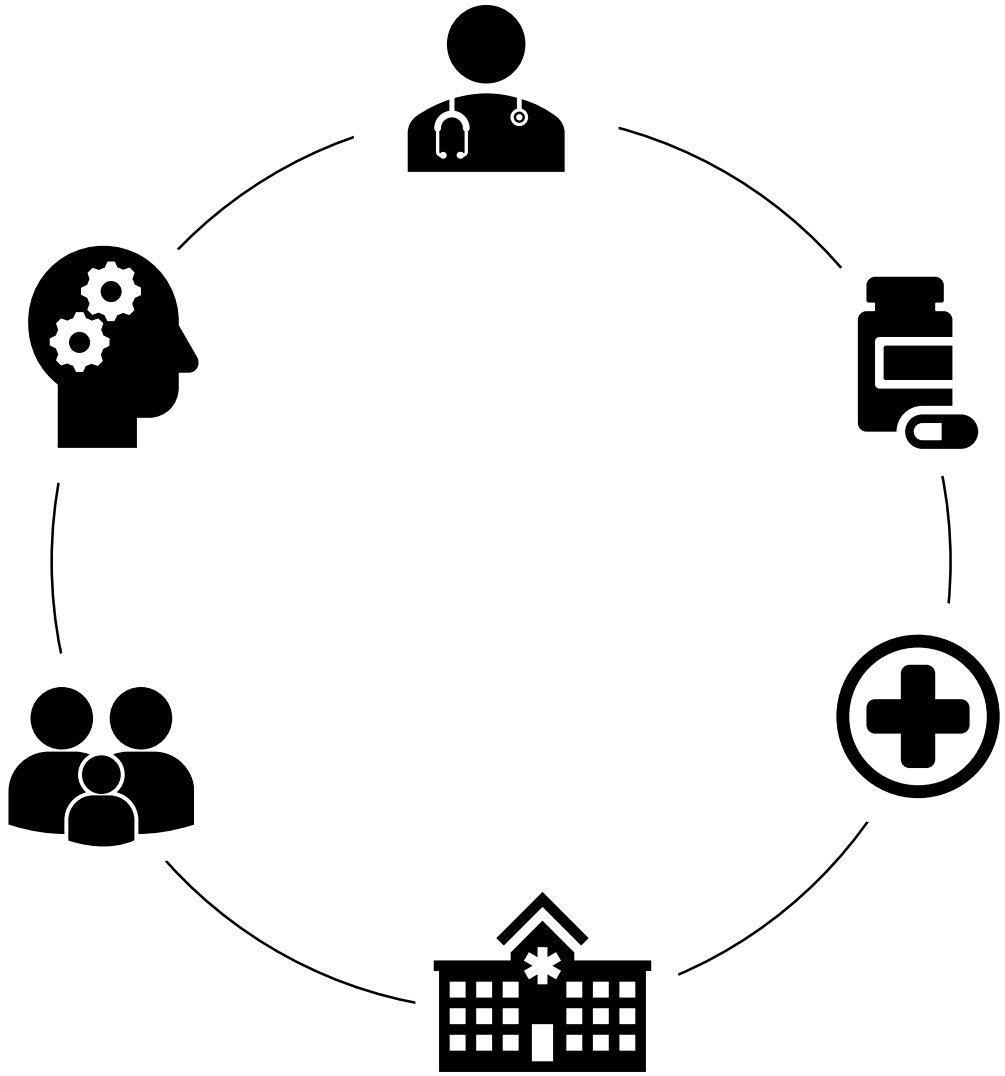
"Adesão ao tratamento medicamentoso deve ser considerado como um comportamento

complexo e multifatorial,

que expressa, no nível fenotípico, o resultado da interação entre um

fluxo de interrelações

que ocorrem de forma sistemática entre **numerosos fatores causais específicos e numerosos fatores moderadores** modificáveis ou não que se sobrepõe"



Fatores associados à famíla e à sociedade

Pacientes apontam **estigma** como um dos fatores mais importantes para não usar medicação.

Família pode atenuar ou amplificar o efeito do estigma da comunidade.

Estigma e preconceito são obstáculos para apoio na tomada das medicações

Psicoeducação a nível individual, familiar e coletivo

Abordagem coletiva para diminuição do estigma mostram pouco impacto

Tomada supervisionada da medicação mostra efeito positivo na adesão

Abordagem com a família em uma terapia em grupo ou a nível individual para diminuição do estigma

Fatores associados ao sistema

Custos das medicações

No sistema público:
Dificuldade de acesso ao atendimento
Atendimentos breves
Tempo longo para follow-up

Lista de medicações disponíveis, preferência por medicações genéricas, burocracia para medicações de alto custo, limite para medicações prescritas

Discutir custos com paciente e familiares

Flexibilização nas políticas públicas que resultam em restrições ao tratamento

Tratamento por ordem judicial

Tratamento assertivo na comunidade

Monitoramento eletrônico

Fatores associados ao médico

Pouca experiência com psicoses, levando ao uso de polifarmácia e doses excessivas das medicações

Pouco investimento na relação médico-paciente

Evitar o uso de **polifarmácia e superdoses**

Investimento na construção de uma **forte aliança terapêutica**

Envolvimento das preferências do paciente na escolha da medicação

- **Participação ativa na escolha da medicação, inclusive na possibilidade de uso de depot**

Fatores associados ao paciente

Alguns traços de personalidade influenciam na tomada de medicações, principalmente, busca por novidades e desinibição.

Atitudes negativas com a medicação

Psicoeducação

Entrevista motivacional

Terapia cognitivo comportamental

Uso de incentivos financeiros

Fatores associados à doença

Sintomas depressivos e uso de substâncias

Comprometimento cognitivo

Sintomas psicóticos mais severos

Crítica ruim

Tratar comorbidades adequadamente

Uso de auxílio eletrônico ou analógico

Psicoterapia
Entrevista motivacional
Terapia cognitivo comportamental

Tratamento involuntário
(apesar de não haver evidência de melhora na adesão a longo prazo)

Abordar, de forma direta e sem julgamentos, a questão da adesão com o paciente. Perguntar sobre efeitos colaterais e opiniões sobre as medicações

Fatores associados à medicação

Diferenças entre medicações antipsicóticas
Melhor tolerabilidade de APs de 2ª geração

Menor eficácia e menor tolerabilidade

Maior complexidade do tratamento

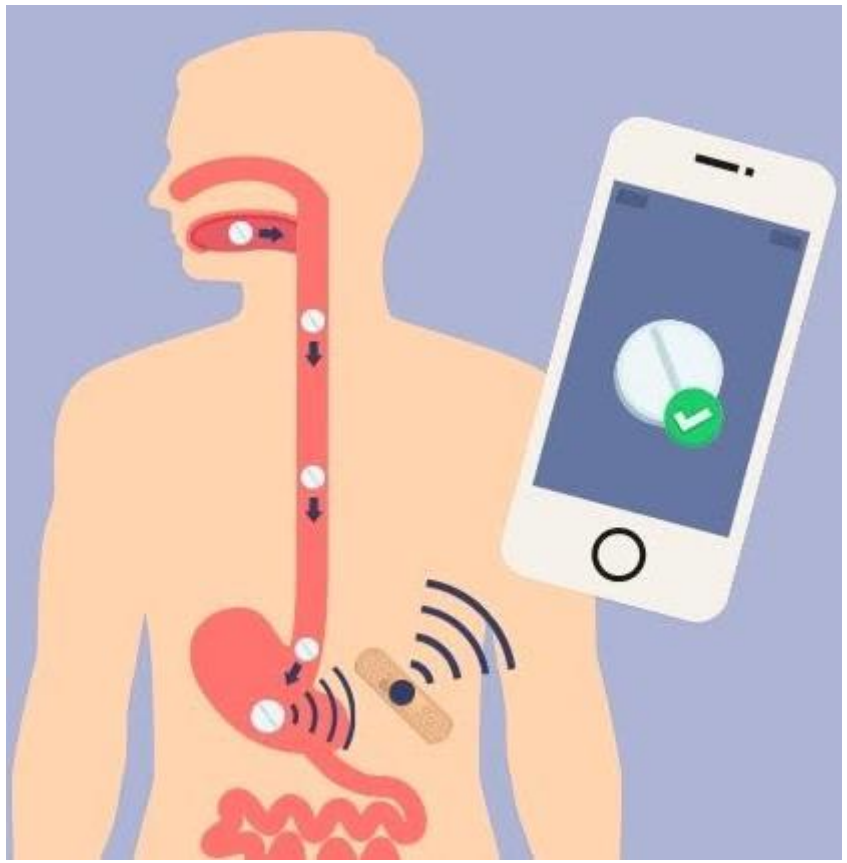
Dose da medicação?

Evidências de efeitos pequenos a moderados associados à escolha da medicação

Atenção aos efeitos colaterais

Simplificar a posologia das medicações - Diminuição da frequência de tomada de medicação


Abilify MyCite®
(aripiprazole tablets with sensor)
Dispense the accompanying Medication Guide to each patient.
Needs a compatible mobile device.
Please see U.S. FULL PRESCRIBING INFORMATION including Boxed WARNING enclosed.
Keep Abilify MyCite® components out of the reach of children.
5 mg
30 Tablets
Abilify MyCite
Rx only
5 mg

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Medisafe

Uso de medicações de depósito

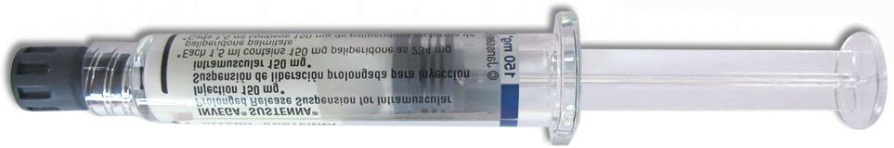
- Não devem ser usadas rotineiramente de forma **coerciva**
- Não existe evidência de melhora na adesão a curto prazo
- **A longo prazo**, apenas em estudos naturalísticos, se observa melhora de desfechos: hospitalização e recaída
- Quando é atingido o **steady-state** observamos menor variabilidade nas concentrações plasmáticas -> diminuição de efeitos colaterais
- Facilitam a diferenciação entre **má adesão e ineficácia neuroléptica**
- Após estabilidade, sempre considerar **redução da dose** (a cada 3 – 6 meses)
- Entre as formulações, **não há diferença de efetividade, apenas tolerabilidade**

Dicas para uso de medicações de depósito

- Para APs de 1ª geração usar uma **dose teste**
- Iniciar com a **menor dose** licenciada (pouca evidência de relação dose-resposta)
- Usar o **máximo intervalo** permitido entre as doses (demora 3-6 meses para piora sintomática)
- Ajustar a dose apenas após **período adequado** (> 1 mês)
- Não é recomendado iniciar com depósito sem avaliar a **tolerância à medicação oral** por, pelo menos, 2 semanas

Medicamento

INVEGA® SUSTENNA®
palmitato de paliperidona
suspensão injetável de liberação prolongada



100mg/ml
50mg, 75mg, 100mg e 150mg

At 2ª gen Metabólito ativo da Risperidona
Antagonista: α_1, α_2, D_2, H_1, and $5\text{-}HT_{2A}$

Farmacodinâmica

Pico plasmático: 13 dias
Meia-vida: 24-45 dias
Steady-state: 20 semanas

Quanto custa?

50mg - PMC/SP **R$ 1.320,26**
75mg - PMC/SP **R$ 1.717,47**
100mg - PMC/SP **R$ 2.110,64**
150mg - PMC/SP **R$ 2.110,64**

Como usar ?

Dose recomendada: **50 – 150mg/mês**
Frequência: mensal
Deltóide ou Glúteo
Não é necessário dose suplementar
É necessário fazer Loading
Dia 1 – 150mg (Deltóide)
Dia 8 (±4d) – 100mg (Deltóide)
Após 30d – 50 -150mg

Risperidona 3mg/d → 75mg/mês
4mg/d → 100mg/mês
6mg/d → 150mg/mês

Medicamento

INVEGA TRINZA®
palmitato de paliperidona suspensão injetável liberação prolongada

175mg, 263mg, 350mg, 525mg

Recomendado apenas para pacientes estáveis com Invega Sustenna por 4 meses ou mais sem necessidade de ajuste de dose.

Medicamento

ZYPAdhera®

ZYPREXA Relprevv®
(olanzapine) For Extended Release Injectable Suspension

Liberação aguda e sustentada
Frequência mensal
Meia-vida: 30 dias, Pico em 3 dias
"Post-injection syndrome": sonolência e delirium. Medicação só pode ser aplicada em ambiente hospitalar e é necessário 6 horas de observação

Medicamento

Abilify Maintena®
(aripiprazole) for extended release injectable suspension

ARISTADA INITIO®
aripiprazole lauroxil
extended-release injectable suspension
675 mg

+

ARISTADA®
aripiprazole lauroxil
extended-release injectable suspension
441 mg | 662 mg | 882 mg | 1064 mg

Não possui os efeitos colaterais metabólicos ou associados à prolactina
Frequência mensal. Meia-vida: 30 dias
É necessário suplementação oral por 2 semanas

Medicamento

Risperdal CONSTA

risperidone Long-Acting Injection

12.5mg, 25mg, 37.5mg, 50mg

SUS

At 2ª gen Antagonista: D1, D2 e 5-HT_{2A}

Farmacodinâmica

Pico plasmático: 30 dias
Meia-vida: 4 dias
Steady-state: 8 semanas

Quanto custa?

25mg - PMC/SP **R$ 1.088,55**
37,5mg - PMC/SP **R$ 1.405,03**
50mg - PMC/SP **R$ 2.025,24**

Como usar ?

Dose recomendada: **25 – 50mg/2sem**
Frequência: 2 semanas
Deltóide ou Glúteo
Necessário dose oral suplementar (3-8sem)
Troca de depot 1ª gen não é recomendada
Menor taxa de descontinuação

Risperidona	2mg/d -> 25mg/2sem
	4mg/d -> 50mg/2sem
	6mg/d -> 75mg/2sem?

Medicamento

SUS

T Classe dos tioxetanos
Antagonista: D1, D2, H_1 e 5-HT_2

Farmacodinâmica

Pico plasmático: 4-7 dias
Meia-vida: 19 dias
Steady-state: 12 semanas

Quanto custa?

Clopixol Depot
200mg - PMC/SP **R$ 85,43**
Clopixol-Acuphase
50mg - PMC/SP **R$ 42,81**

Como usar ?

Dose recomendada: **200mg/2sem**
600mg/sem

Frequência: 2-4 semanas
Glúteo ou Coxa
Iniciar com Acu-phase 50-150mg (3 dias)

Acu-phase 50mg/3d → 100mg/2sem
100mg/3d → 200mg/2sem
150mg/3d → 300mg/2sem

Medicamento

SUS

HALOPERIDOL DECANOATO 50mg/ml

T Bloqueia receptores D2 de forma não seletiva

Farmacodinâmica

Pico plasmático: 7 dias
Meia-vida: 21 dias
Steady-state: 14 semanas

Quanto custa?

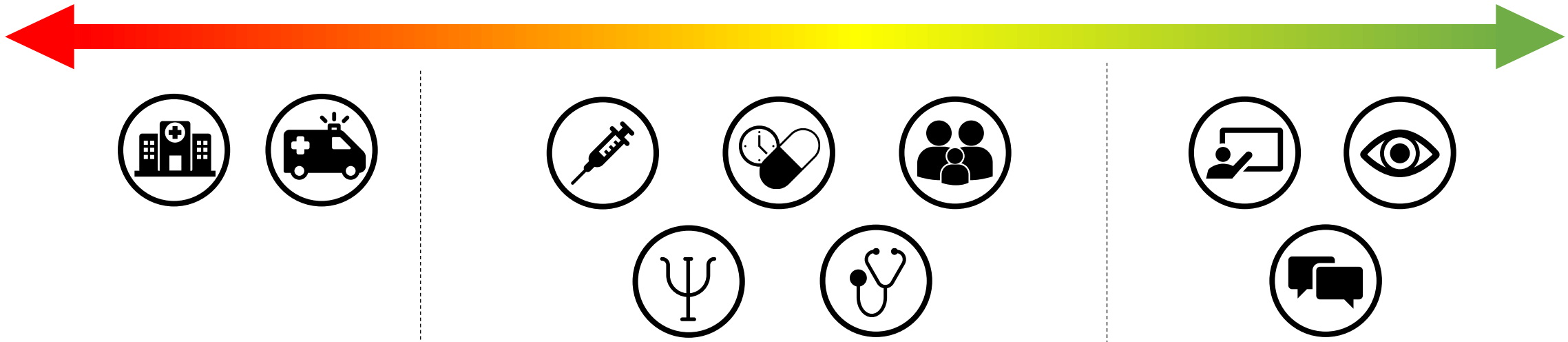
5 AMPs - PMC/SP **R$ 136,61 (R)**
36 AMPs - PMC/SP **R$ 762,54**
(R$ 20 – 30 / AMP)

Como usar ?

Dose recomendada: **50 – 300mg/mês**
Frequência: mensal
Glúteo
Necessário dose oral suplementar (1sem)
Altas taxas de sintomas extrapiramidais
Inicial: Haldol VO 10 – **20x**
Dose inicial máxima 100mg, administrar o restante em 3-7 dias
Esquema de Loading 300mg/2sem e dosar

Má adesão
Sintomas graves
Crítica ausente

Boa adesão
Sintomas leves
Crítica Presente



(Coerção)

(Persuasão)

(Dialética)

Involuntária/
Compulsória

Voluntária

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OBRIGADO!

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