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Schizophrenia – Shared Decision-Making: Implications for Adherence and Relapse Prevention

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Dr. Kane is a recipient of the Arthur P. Noyes Award in Schizophrenia, the NAPPH Presidential Award for Research, the American Psychiatric Association Foundation's Fund Prize for Research, the Kempf Fund Award for Research Development in Psychobiological Psychiatry, the Lieber Prize for Outstanding Research in Schizophrenia, the Heinz E. Lehmann Research Award from New York State, and the Dean Award from the American College of Psychiatrists.

This publication is a summary of a recent webstream presentation by John Kane, Professor of Psychiatry, Neurology and Neuroscience, Albert Einstein College of Medicine, Yeshiva University, New York, USA. He addressed psychiatrists, nurses and pharmacists in Australia and New Zealand in June 2010 about shared decision-making and long-term outcome in patients with schizophrenia.

Adherence to medication

The problem of non-adherence to medication in general, not just to antipsychotics, is the focus of a review published in 2005.[1] As the review's authors point out, the terms we use to describe this phenomenon are not ideal. When we talk about adherence (or compliance with) a medication regimen, i.e. the extent to which patients take medications as prescribed by their health care providers, the word "adherence" implies a problem in behaviour; i.e. patients are behaving badly when they are not adherent or compliant with their medication. In Professor Kane's view, the key element is that this phenomenon is largely a part of human nature and we must be careful to avoid approaching our patients in a pejorative way, to avoid stigmatising them and implying they are behaving badly. After all, most people with chronic illnesses have difficulty taking medication on a regular basis, notes Professor Kane.

A recent paper described common misconceptions about adherent behaviour and described the following 10 tenets:[2]

1. Patients do not typically communicate their adherence intentions to their health care providers. It is information that we need to try to elicit from them and understand what the potential obstacles are.
2. Most health care providers just assume that *their* patients are adherent; we prefer to think that other health care providers have patients who will not take medications as prescribed, whereas ours are adherent.
3. A 'non-adherent personality' does not exist.
4. Adherence to prescription medications behaviour is largely unrelated to adherence to self-care and lifestyle recommendations.
5. There is no consistent relationship between demographic characteristics and adherence.
6. Patients want information about their prescription medications and will feel frustrated if not enough information is provided to them.
7. Health care providers are inconsistent communicators about prescription medicines.
8. Medication-taking is a decision-making process, and patients actively make decisions about their medications.
9. Non-adherence is rational behaviour – it is driven by patient beliefs about their treatment, disease, and prognosis as well as their objective experiences with their treatment and disease.
10. Adherence represents shades of grey – patients can be faithfully adherent to one medication, non-fulfill on another, and be non-persistent to another because they hold different beliefs about medications to which they adhere, non-fulfill, and non-persist.

A review of studies of medication adherence for antipsychotics, antidepressants, and various non-psychiatric medications has indicated different levels of adherence among various agents.[3] A total of 24 studies (lasting 3–24 months) involving antipsychotics, patients took an average of 58% of the recommended quantity of medication, while in 10 studies (1.5–12 months) prescribing antidepressants the patients took approximately 65% of the recommended amount. In 12 studies (0.25–10 months) involving patients with non-psychiatric disorders (e.g., hypertension, hyperlipidaemia, or epilepsy), the average adherence rate was 76%.

Professor Kane noted that while adherence is evidently a problem across disease states, it may be even more problematic in schizophrenia because of its many associated challenges, such as stigma, lack of insight and cognitive impairment, among others.

Partial compliance in schizophrenia begins early

Evidence documents that within merely 7–10 days of discharge from hospital, up to as many as 25% of patients with schizophrenia have difficulty taking their medication on a regular basis.[4] At 1 year, as many as 50% of patients are having difficulty and by 2 years, the proportion can be as high as 75% who are not taking their medication on a regular basis.[5] Professor Kane contends that such data highlight the fact that it is the average patient who is having difficulty taking the medication, not the exception, and this phenomenon occurs early on in the prescribed medication regimen.

Another important consideration is that patients do not have to be non-adherent for long periods of time, to suffer adverse consequences of non-adherence. In data from over 4,000 patients from a California Medicaid assessment of refill compliance using pharmacy records, even patients who miss as few as 10 days or less of antipsychotic medication significantly increase their risk of hospitalisation.[6] Notably, as the gap in medication compliance increases, so does the risk of hospitalisation, in a linear fashion. Professor Kane emphasised that it does not take a long period of non-adherence to increase the risk of hospitalisation.

Drug holidays increase suicide attempt rate

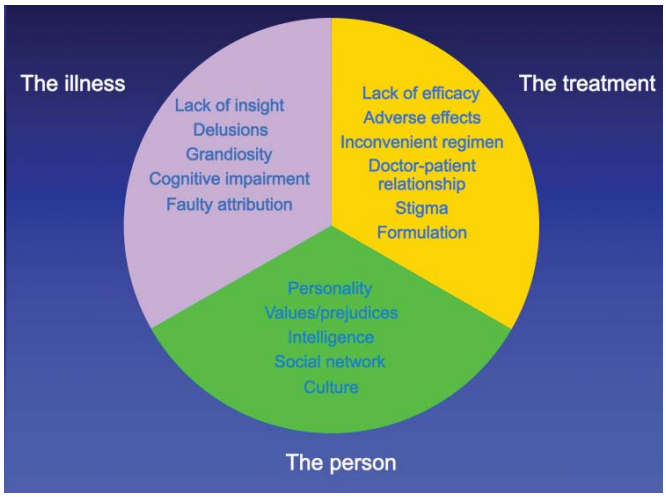
A study from The Netherlands examined drug-dispensing data linked to hospital discharge records for 603 patients with schizophrenia, 204 (33%) of whom interrupted atypical antipsychotic treatment for at least 30 days.[7] After adjusting for age and gender, there was a four-fold increased risk for attempting suicide among patients with drug holidays compared to patients without drug holidays ($RR_{adjusted\ for\ age\ and\ gender}$ 4.2; 95% CI 1.7 to 10.1). Professor Kane noted that this is just one example of the consequences that can arise from gaps in medication adherence.

When psychiatrists were surveyed in 1998 as to what they saw as major challenges in the treatment of schizophrenia, they ranked non-adherence as their greatest challenge, followed by lack of efficacy.[8] Clearly, non-adherence is a major concern for clinicians.

Factors contributing to non-adherence

Some of the factors contributing to non-adherence have been categorised by three different domains; the illness, treatment, and the person, as shown in Figure 1. Illness-related factors such as lack of insight and cognitive impairment significantly impact treatment adherence, while various treatment-related aspects including lack of efficacy, adverse effects, and patients' unrealistic expectations of treatment efficacy, will likewise greatly impact on adherence. The doctor-patient therapeutic alliance has an important role to play in treatment adherence, noted Professor Kane.

Figure 1: Factors contributing to non-adherence



Overestimation of treatment adherence

Psychiatrists have been documented as reporting much higher levels of adherence or compliance (i.e. missing <20% of medication) among their patients (around 43%) than are generally reported by the literature (considerably lower at 28%).[9] Again, this underscores the belief held by many clinicians, who contend that their patients are much more compliant that the patients of other clinicians. Such assumptions are unrealistic, says Professor Kane.

Similarly, as Lam and colleagues have demonstrated, patients can have unrealistic perceptions of their level of compliance: survey data presented in 2003 show that while as many as 68% of patients will claim that they are taking all their medications, pill counts reveal a compliance level of merely 10%.[10] Data from a survey of clinicians, as reported by Byerly and colleagues, reveal that up to 95% of clinicians will predict that their patients are taking over 70% of their medications as prescribed, when electronic monitoring of medication doses showed that only 38% of those patients were compliant.[11]

Consequences of non-adherence

Approximately 50% of patients who discontinue/do not take antipsychotics will relapse within 3–10 months.[12,13] The fact that they do not relapse immediately is a problem because patients can then persuade themselves that if they can do without the medication for a week, a month or more, without relapsing, then they might think that they do not really need it.

Professor Kane stressed that clinicians must ensure that their patients understand the consequences of discontinuing medication – a relapse might occur immediately, or it might not for some weeks or months, but when it does, there are serious consequences. A recent trial involving 50 patients with recent-onset schizophrenia defined good adherence to antipsychotic medication as less than one month without medication.[14] When outcomes for poor and good adherence with oral or depot antipsychotic medication combined were compared over a 24-month follow-up period, as many as 69% of patients with poor adherence relapsed compared with 18% of patients with good adherence. Non-adherence was also associated with being persistently psychotic and with an increased risk of being admitted to hospital.

Recovery in schizophrenia

Recovery in schizophrenia is an important construct. Criteria for recovery, as defined by Liberman and Kopelowicz at the University of California, Los Angeles, encompass the following:[15]

- Recovery criteria must be met in each of four domains
- Improvement in each domain must be sustained concurrently for at least two years
- Level of recovery in these 4 domains is measured by symptom remission, appropriate role function, ability to perform day-to-day living tasks without supervision (e.g. taking a shower) and social interactions (having contact with people outside the immediate family on a regular basis).

When these criteria were applied to a cohort of 118 patients with first-episode schizophrenia or schizoaffective disorder participating in a study undertaken by Robinson and colleagues at The Zucker Hillside Hospital, New York, the overall rate of recovery during the early course of the illness was disappointingly low.[16] Whereas long-term follow-up studies have found that a substantial number of patients with schizophrenia achieve full recovery (i.e., sustained improvement in both symptoms and social/vocational functioning) when examined decades after an index admission, this study assessed recovery over a period of up to nine years after the index episode.

Cumulative recovery rates revealed that very few patients met full recovery criteria for two years or more during their time in the study: rates at 3, 4 and 5 years were 9.7%, 12.3% and 13.7%, respectively.

An earlier analysis of 104 patients from this study demonstrated that the risk for psychotic relapse after recovery is high.[17] Five years after initial recovery, the cumulative first relapse rate was 81.9%; the second relapse rate was 78.0%. By 4 years after recovery from a second relapse, the cumulative third relapse rate was 86.2%. A survival analysis revealed that the risk of a first or second relapse when not taking medication is increased by almost 5 times than when taking medication (HR for an initial relapse, 4.89; HR for a second relapse, 4.57).[17]

Neurobiological consequences of relapse

Besides the psychosocial and vocational consequences of relapse in schizophrenia, serious neurobiological consequences occur with each relapse and are exacerbated by non-adherence to antipsychotics. In a 5-year longitudinal study, whole-brain MRI scans were obtained from 96 patients with schizophrenia and 113 matched healthy comparison subjects.[18] During the 5-year study period, progressive decreases in volume and density in the left superior temporal gray matter were found in patients as compared with controls. Importantly, the progression in left frontal density loss appears to be related to an increased number of psychotic episodes. The number of hospitalisations correlated with superior frontal gray matter density; the greater the reduction in density, the more hospitalisations. Conversely, a higher cumulative dose of clozapine and olanzapine during the scan interval attenuated the progressive decreases of the frontal lobe.

Relapse consequences

The consequences following each relapse can be categorised within three domains – biological, psychological, and social – as listed below:

- Patients may experience more intense psychotic symptoms when admitted following poor adherence
- Neurobiological damage increases cumulatively with each relapse (positive symptoms)
- Each relapse results in an increasingly longer time to remission
- Relapses contribute to psychosocial decline (may be secondary to worsening positive/negative symptoms).

Clearly, the consequences of non-adherence can be devastating:

Psychological consequences include

- Demoralisation
- Hopelessness
- Poor self-esteem
- Increased isolation (1° and 2°)
- Disruption to family
- Increased suicide risk (4-fold increase).

Social consequences include

- More involuntary treatment
- Longer hospital stays (if non-adherent before admission)
- Breaking the thread-like social connections re-established after previous relapses
- Higher direct and indirect costs (services, community, patient, family)
- Increased risk of violent behaviour
- Increased involvement in the criminal justice system due to nuisance or petty crimes
- Increased risk of victimisation.

In a 2003 meta-analysis of data from 3,015 participants in 17 randomised, controlled studies comparing new-generation antipsychotic medications with conventional antipsychotics for the prevention of relapse in schizophrenia, 1-year relapse rates were significantly lower with the newer drugs (a total of 15% of patients on atypicals vs 23% of patients on conventional antipsychotics; p=0.0001 in favour of atypical drugs).[19] Professor Kane noted that not only do the newer atypicals have this apparent advantage over typical antipsychotics in preventing relapse, but in his opinion, another advantage is that the atypicals are associated with a substantial reduction in risk of treatment-related problems such as tardive dyskinesia. In this analysis, the risk of tardive dyskinesia was reduced from 5% per year with cumulative exposure to conventional antipsychotics to 1% per year with atypical antipsychotic cumulative exposure.

Professor Kane highlighted the fact that depot antipsychotics reduce relapse rates, using data from an unpublished meta-analysis by Mentschel and colleagues, in which pooled data from 8 long-term studies demonstrated an overall treatment effect in favour of depot antipsychotics over other antipsychotic formulations (RR 0.78; 95% CI 0.66–0.91; overall effect z=3.06; p=0.002 in favour of depot antipsychotics).

RLAI: advantages over quetiapine

Data presented at the American Psychiatric Association (APA) 161st Annual Meeting in Washington, D.C., 2008, showed that risperidone long-acting injection (RLAI) was associated with a significantly longer time to relapse compared to patients with schizophrenia who were treated with an oral atypical medication, quetiapine.[20] This open-label study involved 710 patients (355 of whom received RLAI and 355 quetiapine) and investigated whether treatment with RLAI compared with oral quetiapine, when tested in a routine care setting within general psychiatric services, had an effect on long-term efficacy maintenance as measured by time to relapse.

Not only was the average relapse-free time significantly longer in patients treated with RLAI compared with quetiapine (607 days vs 533 days; p<0.0001) but furthermore, over the 24-month treatment period, relapse occurred in significantly fewer patients treated with RLAI than the quetiapine treatment arm (16.5% vs 31.3%). Notably, the differences in

relapse rates emerged after only 3 months of treatment and were continuing to diverge at 24 months. In addition, treatment completion rates significantly favoured RLAI (51.7%) over quetiapine (38%; p<0.0004)

This study is just one example of the potential advantages offered by LAI drugs such as the risperidone LAI formulation over conventional oral formulations – it is hoped that a number of blinded studies that are now under way, involving comparisons of RLAI with oral conventional antipsychotics, will replicate these results, noted Professor Kane.

Substantial clinical advantages offered by LAI formulations include the following:

- Assure medication delivery, reliable
- Convenient regimen, freedom from daily medication
- Immediate awareness of non-adherence (injection schedules eliminate uncertainty about adherence, unlike oral dosing schedules)
- Avoid first-pass metabolism (use lowest effective dose)
- Predictable and stable plasma levels
- No abrupt loss of efficacy if dose missed (LAI allows for stable concentrations of the active drug to remain at a therapeutic range for at least a couple of weeks)
- Many patients prefer them.

Various reviews have reported that LAI antipsychotics are viewed favourably by patients, as in the findings published by Walburn and colleagues in 2001, which reported that approximately 60% of patients receiving LAI antipsychotics strongly preferred them over oral typical antipsychotic formulations.[21]

Benefits of LAI antipsychotics

Depot injection formulations of conventional antipsychotics have been associated with significantly lower relapse rates than oral conventional agents in mirror-image studies. A 1994 analysis of depot antipsychotic therapy provided evidence that switching from oral to a depot medication decreases relapses, the number of hospitalisations and percentage of time in hospital.[22]

The benefits of LAI antipsychotics may take time to become apparent. In a comparison of the ability of depot fluphenazine and oral fluphenazine to prevent relapse in a cohort of 105 newly discharged schizophrenic patients, relapse rates were nearly identical in the first year postdischarge for both groups, i.e. 39.5% of the oral fluphenazine group and 35.1% of the depot fluphenazine group relapsed.[23] However, the survivorship curves tended to diverge thereafter, with a decline in the risk of relapse for the depot formulation group over the 2 years of treatment contrasting with a constant rate of relapse continued among patients treated with oral fluphenazine in the second year. By month 24, 64.7% of the oral fluphenazine group versus 40.3% of the depot fluphenazine group had relapsed. Professor Kane noted that since it takes a while for a consequential relapse to occur after stopping medication, this relapse pattern is interesting and suggests that we do need long-term studies to usefully compare LAI formulations with oral medications.

Matching interventions to patient factors

Professor Kane noted that we need to think about the various elements that underlie adherence. He referred to a recent paper that discussed various factors impeding adherence to antipsychotics and proposed ways in which practitioners can better understand this complex issue and implement practical therapeutic interventions that encourage adherence [see Figure 2].[24]

Figure 2: Matching interventions to patient factors[24]

Key Factor	General Clinical Approach	Intervention
Unfavourable attitudes to taking or staying on medication	Routinely assess Emphasise alliance Use patient-centred approach Start with patient's point of view Do not confront with disease model of illness, but stay symptom focused	Motivational interviewing CBT Compliance therapy Family intervention NAMI Family-to-Family
Involving significant others influences willingness to take or stay on medication	Include families and significant others in assessments and interviews	Family psychoeducation NAMI Family-to-Family
Role of persistent symptoms interfere with ability to take medications	Consider symptoms as barrier	Behavioural interventions (e.g., CBT)
Environmental barriers prevent medication access (interacts with persistent symptoms)	Consider treatment environment barriers assuming better symptom control is currently not possible	ACT/PACT interventions Transportation Housing Pharmacy CAT

NAMI, National Alliance on Mental Illness; ACT/PACT, Program of Assertive Community Treatment.

When developing a treatment plan, the various factors that need to be considered include the following:[25,26]

Case management	Case manager ensures that patients receive co-ordinated, continuous, and comprehensive services
Assertive Community Treatment (ACT)	Includes case management and active treatment interventions in an integrated multidisciplinary team approach with a 1:10 staff to patient ratio
Integrated treatment of dual diagnosis	Dual diagnosis denotes co-occurrence of mental illness and substance abuse Combination of mental health and substance abuse interventions tailored to patient-specific needs

In any patient-provider relationship, the strength of the therapeutic alliance is a universal predictor of good outcome. Professor Kane emphasised that establishing a therapeutic alliance is a common goal of *all* psychosocial interventions. The question is: What is the best way to accomplish this goal?

Barriers to an effective therapeutic alliance may include any of the factors below:

- Patient barriers
  - Communication difficulties
  - Off-putting nature of symptoms
  - Shared stigma
- Clinician barriers
  - Underestimating importance of relationship
  - Conveyed hopelessness

Professor Kane noted that **interview style** plays a very important role in the therapeutic alliance; indeed, clinicians need to make sufficient time for an interview, to make certain that they understand how the patient thinks about medications – that patients are not simply stating what they think clinicians want to hear. Clinicians should explain to the patient that they want to hear what the patient really thinks. If clinicians want to respond, Professor Kane suggested that they do not try to do too much, and they should not go beyond what the patient can accept for at that time. As much as possible, keep the discussion about medication adherence positive – even enjoyable. Above all, try to maintain and even strengthen the alliance, even if there is disagreement.

Interventions designed to improve antipsychotic adherence in patients with schizophrenia include educational, behavioural, and environmental approaches, as detailed in Figure 3.[27] The literature documents the greatest improvement in adherence with interventions that combine educational, behavioural, and affective strategies, resulting in additional secondary gains such as: reduced relapse, decreased hospitalisation, decreased psychopathology, improved social function, gains in medication knowledge, and improved insight into the need for treatment.

Figure 3: Psychosocial strategies that may improve adherence[27]

Educational	Behavioural	Environmental
Provide information about disease state	Simplify regimens and use adherence aids	Facilitate a supportive environment
Inform the patient about the purpose and potential side effects of medications	Enable cognitive restructuring of attitudes toward medication and disease state	Encourage counselling and family reporting of adherence to antipsychotic therapy
	Empower patients and caregivers to be active in managing disease	Understand the role of significant others
	Understand the patient's attitudes about medication (reasons for adherence/ non-adherence)	Understand environmental barriers to adherence (e.g. costs, access, etc.)
	Understand the role of symptoms as barriers to adherence	

Expert Consensus Guidelines have provided recommendations intended to improve adherence, within the pharmacological, psychological, and programmatic domains:[25]

Pharmacological:

- Base choice of medication on the side effect profile most acceptable to the patient.
- Consider using a long-acting depot antipsychotic, particularly if the patient has lack of insight into the need for medication.
- Monitor symptoms and side effects.
- Monitor medication (e.g., direct observation, weekly pill box).

Psychological:

- Family education and support.
- Patient education and support.
- Motivation interviewing (e.g., helping the patient realise that attaining personal goals requires compliance with treatment.
- Introduce new interventions gradually according to the level of clinical recovery and cognitive impairment.
- Time interventions based on patient's preference and sense of urgency.

Programmatic:

- Concurrent treatment of substance abuse.
- Provide assertive community treatment services.
- Continuity of primary clinician across treatment modalities (e.g., inpatient, outpatient, and residential programmes).
- Provide a depot medication clinic.
- Provide more intensive services (e.g., case management, day hospital).
- Supervised residential services.

Strategies for improving outcome

Various strategies that may be employed for improving outcome include:

Family psychoeducation

Assertive Community Treatment (ACT)

Schizophrenia treatment algorithms

Disease management programmes

Familiarity with expert consensus guidelines.

Measurement-based decision making – Professor Kane emphasised that it is crucial for clinicians to understand the severity of illness-related symptoms and of side effects related to medications, to understand them from the patient's point of view – this increases the odds of achieving:

Medication adherence goals

Shared decision-making

Provider partnerships

Field case managers

Intensive case management.

Further, it is important to involve the patient's family in the treatment plan, so that they understand the benefits and goals as to what the medication is meant to achieve. Engaging the patient and family supports the medication algorithm and enables them to understand what to expect and how to manage side effects. The family needs to understand and support the concept of a healthy lifestyle for the patient.

A computerised decision support system is important not only for physicians, but also potentially for patients. Family psychoeducation, supported employment/education, as well as individual resiliency training, are additional factors that need to be considered by clinicians in their management of patients.

Shared decision-making

Shared decision-making is an important element of contemporary mental health care and treatment planning. When consumers are given the opportunity to choose interventions according to personal preferences and recovery, this increases the likelihood of these interventions enhancing personal meaning, satisfaction and quality of life.[28] Shared decision-making is a critical component of recovery from mental illnesses, reflecting the psychiatric rehabilitation field's focus on the importance of choice and self-determination.

Researchers have examined the advantages and disadvantages of shared decision-making in health and mental health care:[28]

Advantages

- Practitioners can best obtain relevant information on illnesses and interventions.
- Clients can best make decisions because of the unique values they place on outcomes and the necessary trade-offs based on preferences and needs.
- Shared decision-making is a self-evident right because each person should determine what happens to their body.
- Surveys demonstrate near universal client desire for healthcare information and to participate in treatment decision-making.
- Shared decision-making leads to improvements in the practitioner-client relationship and health outcomes, such as treatment adherence, treatment satisfaction, and biomedical outcomes.
- A shared decision-making orientation can be very effective in promoting consumer engagement in and responsibility for his or her care. This may generalise to other facets in an individual's recovery plan.
- An interaction of mutual respect is fostered and modelled. This can be a confidence builder for consumers.
- Shared decision-making can be empowering to individuals.

Disadvantages

- The plethora of choices could be overwhelming to those who have difficulty with decisions and result in a sense of lost opportunities.
- Clients may experience regret or reject options to spare themselves the possibility of regret.
- There is difficulty in valuing outcomes because clients cannot foresee how they will adapt to illness.
- The anticipation of choice and control may lead to disappointment when expectations meet clinical realities.
- Consumers may be concerned about making a physician or provider angry if they do not choose the recommended course of treatment.
- Consumers who have the expectation that professionals will tell them what to do may become frustrated with the latitude in choosing a course of treatment.

Conclusions

Professor Kane holds that it is incumbent upon physicians to discuss health care choices with patients in a comfortable and effective manner that engages them in decision-making and in a way that is responsive to their needs, levels of understanding and preferences, tailoring discussions about medication to each individual patient. In order to promote treatment adherence, it is critical that patients are appropriately engaged in the therapeutic alliance and decision-making forum. Adherence is one of the biggest challenges that we face in all of health care, in Professor Kane's opinion. It is imperative that we understand the obstacles to adherence and ensure that we work through those obstacles, so that patients can benefit from the medications that we have developed and provided for them.

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Professor Kane acts as a Consultant and is on the Advisory Boards of several pharmaceutical companies that develop antipsychotic medications, including Janssen Pharmaceutica, for which he is also on the Speakers Bureau. An educational grant from Janssen-Cilag Pty Limited supported the publication of this article. The content or opinions expressed in this publication may not reflect the views of Janssen-Cilag.