Expert Opinion

Addressing the need for increased adherence to multiple sclerosis therapy: can delivery technology enhance patient motivation?

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Background: Several injectable disease-modifying drugs are available for the treatment of multiple sclerosis (MS) to control disease progression and reduce relapse frequency and severity. However, the benefits offered by treatment may be compromised by suboptimal levels of adherence to prescribed regimens. *Objective*: To examine what is now known about adherence to MS therapies, and to discuss how technological advances may affect adherence in the future, with reference to examples from other therapy areas. *Results*: Perceived lack of efficacy and therapy-related adverse events are important factors influencing poor adherence. Comprehensive patient education and support are vital in maintaining adherence to MS therapies. Also, improvements in the tolerability, convenience of administration and patient acceptability of MS therapies may enhance adherence. This may be achieved by adjustments to drug formulation and the use of injection devices. Auto-injector devices have been shown to reduce the incidence of injection-site reactions and discomfort in patients with MS, and it is hoped that improvements in delivery technology may further enhance patient motivation to remain adherent to MS therapy in the future. The most recent advance in injection-delivery technology is the development of electronic devices, which can be adjusted for comfort and record dosing history. *Conclusions*: Few studies have directly addressed adherence to MS therapy and further clarification is required. Adjustments to drug formulation, provision of patient education and improvements to injection devices may all contribute indirectly to improved adherence in the future.

Keywords: auto-injector, drug delivery, multiple sclerosis, self-injection, skin reaction, treatment adherence

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1. Introduction

To gain the full potential benefit from a therapy, patients need to adhere to their prescribed regimen. The term 'adherence' is preferred to 'compliance' because it recognises the patient as the driver of treatment success, thus empowering the patient as a key decision-maker in the treatment process. The concept of adherence requires the individual to accept the necessity for the medication and to persist with the therapy, but the term compliance refers only to the requirement that the patient follows instructions [1]. The World Health Organisation (WHO) defines adherence as 'The extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider' [2].

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The degree to which patients adhere to medication regimens is difficult to assess and quantify accurately. There is no standardised toolkit for the measurement of adherence and most studies that have adherence as an outcome use indirect measures. Study protocols can include adherence as a patient-reported outcome, but such results may be unreliable as many patients tend to overestimate their degree of adherence [3]. Another approach is for study staff to calculate adherence rates by counting residual pills, cartridges or delivery devices. Although this is a simple method, the results may not be accurate because patients may discard items in an effort to increase their apparent level of adherence. Data from the pharmacy or supplier are more reliable and can allow assessment of a large number of patients. However, information is provided only on how much of the medication was supplied to patients, not whether the medication was taken appropriately or the device used properly. Medication monitoring systems are reliable and can identify, and record, the time and date of each dose. Advances in injection-device technology now allow monitoring systems to be integrated into the device, which means that it will become easier to gain a true insight into adherence to injectable therapies.

It is clear that poor adherence is an important worldwide problem. The WHO quotes an average figure of 50% for adherence to medication for chronic diseases in developed countries; in developing countries the rates of adherence are even lower [2]. For example, rates of 62 – 64% for adherence to insulin regimens have been reported in individuals with type 2 diabetes [4], and a much lower adherence rate (36%) has been reported for some oral diabetes treatments [5]. Suboptimal adherence is likely to affect adversely health outcomes and healthcare costs. Strategies to improve adherence are considered to be a powerful means of improving outcomes, with Haynes *et al.* commenting that increasing adherence may 'have a far greater impact on the health of the population than any improvement in specific medical treatments' [6].

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory, degenerative disease of the central nervous system. Although several therapies are available to control disease progression in MS, there is, as yet, no cure. Therefore, patients with MS require long-term treatment, without 'treatment holidays', as interrupted therapy leads to the reappearance or worsening of disease activity [7,8]. This review explores factors influencing adherence to MS therapy, and details strategies that can be used to improve adherence rates, with particular regard to continuing developments in drug-delivery technology. Also, the advancements in delivery technology in other therapy areas are considered in terms of how they may be used as an example in the treatment of MS.

2. Adherence to MS therapy

A diagnosis of MS presents many challenges to both patients and healthcare teams. MS has an extremely variable course and the prognosis for an individual patient is, at present, difficult to predict. There are no curative treatments for MS, although current disease-modifying drugs (DMDs) can reduce the rate of acute neurological attacks and delay disease progression. Also, specific MS symptoms can be managed individually. At present, all first-line DMDs for MS require parenteral administration, with frequency of dosing varying from once daily to once weekly. For a variety of reasons, which will be outlined below, levels of adherence to DMD treatment tend to be lower than optimal.

A recent survey that investigated non-adherence to DMDs for MS, found that ~ 40% of patients were non-adherent (defined as having missed one or more injections in the previous 4 weeks) [9]. Although further data are sparse in terms of the proportion of injections actually administered, rates of treatment discontinuation may be reviewed as a proxy measure of adherence. **Table 1** [10-13] shows the rates of discontinuation reported in four studies that followed patients in the clinical setting. Nearly three-quarters of participants (73%) in a longitudinal prospective study of adherence to DMDs for MS missed at least one dose of medication during follow-up (mean length, 2.4 years) and in any 6-month follow-up period 10% of patients missed > 10 doses [14]. In general, rates of persistence with therapy are higher in clinical trials than in clinical practice, as trial participants tend to be highly motivated, receive more encouragement to use their therapy according to the protocol, and receive a more thorough follow-up. In the everyday clinical setting, patients are more likely to be challenged by factors that can impact negatively on their motivation to adhere to therapy. Poor adherence can have a negative influence on treatment outcomes. Patients with MS who have long gaps in their treatment regimens have a higher risk of relapse than those with better adherence [14].

3. Factors influencing adherence to MS therapy

3.1 Injection-related psychological issues

The current first-line DMDs for MS are: IFN (interferon)-β_{1a}, administered either subcutaneously (s.c.) three times weekly or intramuscularly (i.m.) once weekly; IFN-β_{1b} s.c. every other day; and glatiramer acetate (GA) s.c. daily. The fact that all current DMDs for MS require parenteral administration causes difficulty for some patients, and can contribute to suboptimal levels of adherence and treatment persistence [15,16]. Many people dislike injections, particularly when they are self-administered [10]; the prevalence of injection phobia in the general population is 7–22% [17]. Self-injection anxiety and belief that self-injection is not possible have been shown to be strong predictors of medication discontinuation at 6 months [18]. The autonomic reactions that can precede an injection can reinforce the tendency to avoid injecting, and fear of injections can also stem from mistaken beliefs regarding the associated risks. Common fears encountered with injections include

Table 1. Rates of discontinuation from disease-modifying therapy for multiple sclerosis in clinical practice.

Report	Medication	Follow-up	Discontinuation rate of patients (%)
Tremlett and Oger 2003 [10]	IFN-β	> 3 years	39 (79/203)
O'Rourke and Hutchinson 2005 [11]	IFN-β	4 years	28 (109/394)
Rio *et al*. 2005 [12]	IFN-β or GA	4 years	17 (107/622)
Portaccio *et al*. 2008 [13]	IFN-β	4 years	46 (104/225)

GA: Glatiramer acetate; IFN: Interferon

causing an embolism by injecting an air bubble, puncturing a vein, touching a bone and damaging muscle [17].

3.2 Perceived lack of efficacy

To remain motivated and adhere to therapy, patients need to believe in the value of their treatment and the benefits it confers. Patients who believe their treatment is not working (even if this is not true) are at risk of poor adherence, or of discontinuing treatment altogether. Perceived lack of efficacy has been reported to be the cause of 30% of interruption in first-line treatment in MS [10].

The unpredictable and varied disease course of MS means that it may be difficult for patients to appreciate fully the importance of staying on treatment. Furthermore, although a patient's disease progression may be slowed by therapy, relapses may continue and new symptoms develop. This can negatively affect patients' motivation to continue with treatment, particularly if they had overoptimistic expectations at the start of treatment. A study of patients' expectations of the effects of IFN-β_{1b} treatment reported that 57% of patients had an unrealistic expectation of therapy with regard to relapse reduction, and 34% with regard to improvements in functional status [19].

3.3 Adverse reactions to therapy

'Flu-like' symptoms, depression, injection-site reactions and elevated levels of liver enzymes are among the most commonly reported adverse events in patients treated with IFN-β [20-22]. For those treated with GA, the list includes injection-site reactions, vasodilation, tachycardia, tremor and depression [23]. Lipoatrophy at injection sites has also been associated with GA treatment [24]. The occurrence of adverse events is a major barrier to adherence to MS therapy [10]. A study on patients who stopped or switched IFN-β therapies examined the reasons behind interruptions of > 1 month. The most common reason was perceived lack of efficacy (30% of patients), followed by injection-site reactions (12% of patients) and 'flu-like' symptoms (10% of patients) [10]. Another study found that patients who discontinued treatment because of adverse events tended to do so sooner after therapy initiation (median 13 months) than those who did so because of perceived lack of efficacy (median 35 months) [11].

It is therefore important to avoid or manage adverse events when possible, with the aim of improving adherence. The 'flu-like' symptoms that can accompany IFN-β therapy tend to be transient, can be mitigated by dose titration at treatment initiation, and are commonly effectively managed with concomitant administration of non-steroidal anti-inflammatory drugs [25]. The incidence of injection-site reactions can be reduced with correct injection technique and by the use of injection devices [26,27]. The impact of improvements to injection technology in MS treatment is discussed in more detail below.

3.4 Disease-related causes of non-adherence

Certain characteristics of the patient and their MS may influence their likelihood of adherence to therapy. Preliminary results from a multivariate analysis of data collected from patient questionnaires reveal lower adherence to therapy in patients who were diagnosed at an early age, patients who perceive their health as poor or fair, and patients using prescription medications for fatigue [28]. A higher degree of disability at the time when treatment is started is also predictive of treatment interruption [12].

In many patients, MS causes cognitive deficits that may affect memory, and a reduction in fine motor skills can affect patients' ability to prepare and administer the injection. Both of these consequences of MS may increase the likelihood of non-adherence. This emphasises the importance of the investigation of cognitive impairment in MS, and the potential for therapy to minimise its impact on patients. Recent research has shown that treatment with s.c. IFN-β_{1a} may be effective against cognitive decline in patients with relapsing MS [29]. Efficacy in delaying cognitive decline has also been suggested for s.c. IFN-β_{1b} [30] and i.m. IFN-β_{1a} [31], although previously reported studies were inconclusive [32].

4. Strategies to help maintain adherence

Clearly, as available drugs have the potential to improve patients' outcomes, it is a key therapeutic goal to ensure that these drugs are used to their full potential. Indeed, it has been speculated that techniques to enhance adherence to

existing therapies may have a greater impact on patient health than improvements to the actual therapies [6]. Patient education and support strategies, improvements in drug tolerability and increased convenience of administration can all contribute to enhancing patient motivation to take medication and thus, potentially, improve disease outcomes. On the other hand, agents with a less favourable safety profile but greater efficacy may command better adherence through their higher degree of efficacy [33].

4.1 Patient education

Patient education programmes are becoming ever more important in the management of chronic diseases. Heightened patient understanding of MS and how it is treated may lead to better adherence to therapy. Specialist MS nurses play a key role in patient support, supplying encouragement to remain adherent to therapy as well as delivering vital training on correct injection technique and the management of MS symptoms and drug-related adverse events. Support and encouragement from the care team, in conjunction with family members and friends, can greatly enhance the patient's motivation to continue with therapy; such motivation can decrease if the patient feels depressed or isolated. Some patients also benefit from contact with groups of fellow patients, where shared experiences may enhance participants' hope and confidence that they can effectively accept and manage their disease in the long term. However, patients who are dissatisfied with their treatment and are less adherent, who may be looking for an alternative to pharmacotherapy, may be inclined actively to discourage fellow patients from remaining adherent.

As mentioned previously, unrealistic expectations regarding efficacy can lead to treatment discontinuation, and patient education is thus vital for managing patients' expectations. One study reported that educational programmes significantly modified unrealistic expectations. However, the results also showed that there is still room for improvement, as 33% of patients maintained their overly optimistic expectations with regard to the reduction in attack rate, despite having been exposed to a training programme [19].

It has been demonstrated that patient education programmes can empower patients with MS and influence their actions [34]. Ideally, such programmes should include information on the unpredictability of MS disease course and the therapeutic options available, including details on the potential benefits and risks of each option. For some patients, being forewarned about the possible appearance of adverse events may have a negative impact, preventing treatment initiation rather than impacting on adherence, but this is unlikely to outweigh the other benefits of patient education, as described above.

It is also essential that patients are made fully aware of the importance of adhering to their prescribed treatment. Patients also benefit from receiving information about potential side effects and how these can be managed [35]. An unexpected complication, in fact, might induce patients to refuse treatment. Taking an active and informed role in treatment decisions may empower patients and, in turn, may enhance their motivation to adhere to treatment.

4.2 Improvements in drug formulation to enhance tolerability

As adverse drug reactions, such as injection-site reactions, can lessen a patient's motivation to inject regularly, it follows that improvements in a drug's tolerability and safety should lead to better levels of adherence. Adjusting the drug's formulation is one way in which tolerability can be improved, with the hope of enhancing adherence. An example of this approach in MS therapy is the new formulation of IFN-β_{1a} for s.c. injection, which is free from human serum albumin (HSA) and fetal bovine serum. A recent study showed that levels of immunogenicity with the new s.c. IFN-β_{1a} formulation were lower than those found with the previous formulation in the EVidence of Interferon Dose–response European–North American Comparative Efficacy (EVIDENCE) and REbif vs Glatiramer Acetate in Relapsing MS Disease (REGARD) studies, but with comparable efficacy. The incidence of injection-site reactions was almost three times lower in patients injecting the new formulation compared with patients using the previous formulation in the EVIDENCE study [36]. Previously, a formulation of i.m. IFN-β_{1a} was developed that did not contain HSA. Low levels of immunogenicity were reported with this formulation, and the safety profile was comparable with the previous formulation of i.m. IFN-β_{1a} [37].

Several oral drugs for MS are in Phase III trials. Orally administered drugs would avoid adherence issues relating to needle phobia or injection-related adverse events. Tolerability and convenience of administration would be the most likely drivers of adherence for these formulations.

4.3 Improvements in drug-delivery devices

Improving the convenience and acceptability of treatment by means of the use of drug-delivery devices is another approach to encouraging patients to adhere to their regimens. Self-injection devices were first introduced in the 1980s for diabetes treatment. Since then, devices for the injection of drugs for various conditions, including MS, have become increasingly sophisticated in an attempt to make them more effective, useful and convenient.

The first insulin pen injector was launched in 1984. Pen injectors allow reliable and accurate dispensing of a drug, but are essentially syringes. Auto-injectors, which became available at approximately the same time, are automated – usually spring-driven – devices that perform the injection. They are used with refillable or prefilled syringes, and therefore usually require a stable liquid-drug formulation. Exceptions are the auto-injectors used for administration of IFN-β_{1b}, the Betaject (BJ) Comfort (Bayer Schering Healthcare AG; Berlin, Germany) and the Extavia injector (Novartis Pharma AG; Basel, Switzerland), both of which require the patient first to reconstitute the

lyophilised drug with the diluent already contained in the syringe. The designs of these systems may not be suitable for patients who have cognitive impairment or reduced dexterity. However, they have the advantage of allowing unrefrigerated storage of the drug for up to 1 month. Some of the first auto-injectors were used for emergency situations only (e.g., the delivery of adrenaline for anaphylactic shock), but in the 1990s, reusable, prefilled auto-injectors for sumatriptan became available for migraine sufferers. Needle-free (gas jet auto-injector) systems and electronic injectors have recently become available in certain indications.

Initially, MS therapies were injected manually, but now, auto-injector devices are available for most of the current first-line therapies, the exception being i.m. IFN-β_{1a}. Prefilled syringes now add to the convenience of administration of all these therapies, although they need to be stored at temperatures between 2 and 8°C and require a lower pH drug formulation for stability, which can cause more pain on s.c. injecton. The added convenience and comfort offered by injection devices may help achieve optimal adherence to medications for chronic diseases. It remains to be confirmed whether injection devices increase adherence to MS therapy, but improvements have been seen in other outcomes (e.g., injection-site reactions and discomfort) [26,27,38]. These improvements may enhance patients' motivation and, subsequently, adherence, and are discussed further below.

Although few studies have directly addressed the effects of delivery devices on adherence to MS therapy, the incidence of injection-site reactions with the different devices, and patient acceptability and preferences, have been reported more often. Delivery of s.c. IFN-β_{1a} using the Rebiject (RJ; Merck Serono SA; Geneva, Switzerland) auto-injector was associated with significantly lower incidence of injection-site reactions than manual injection (78.7% compared with 85.4%) [26]. A randomised crossover study compared the incidence of injection-site reactions in patients treated with IFN-β_{1b} during a month of administration using standard injection technique, followed by 2 months of auto-injector use: 1 month with the BJ, and 1 month with the BJ Lite. The incidence of injection-site reactions was significantly higher when patients used a manual injection technique (35.9%) than when they used the BJ (24.1%) or BJ Light (24.1%) devices. Also, the mean severity score of injection-site reactions (as assessed by physicians) was significantly lower when patients were using either auto-injector compared with the manual injection technique period [27]. A small 1-year observational study of patients with relapsing–remitting MS who were treated with s.c. IFN-β_{1a} found that most patients considered the modified RJ auto-injector (RJII) to be convenient to use, with one-third considering the system easier to use than the standard injection technique. Some participants reported that administration with this auto-injector was associated with less pain and trauma than manual injection [38]. To the author's best knowledge, no published report exists on the Autoject II device used for prefilled glass syringes of GA. Its design is, however, similar to the RJII device.

In five patient surveys and two clinical trials (presented in one paper), it was found that s.c. injection of IFN-β_{1a} was less painful with a thinner, sharper needle than with the standard needle, with some participants reporting that the thinner needle was easier to insert and associated with fewer injection-site reactions [39]. These improvements are reflected in the results of Cramer *et al.*, who showed evidence of significant improvements in all subscales of the MS treatment concerns questionnaire (MSTCQ), including global patient satisfaction (but with the exception of 'flu-like' symptoms), and all pain measures after patients with MS switched from using the RJ auto-injector to the RJII device [40]. The RJII uses a thinner, sharper needle and was designed to enhance simplicity of use. A similar device, with a similarly bevelled needle is used for s.c. injection of GA. The needle used to inject IFN-β_{1b} with BJ Comfort is also thinner than the one used with BJ and BJ Lite.

Although no direct conclusions can be drawn yet regarding the effect of injection devices on adherence to MS therapy, data from the literature in other therapy areas are encouraging. A needle-free injection system for gonadotrophins was associated with high acceptability among women undergoing controlled ovarian hyperstimulation for *in vitro* fertilisation [41]. Although this application differs from MS treatment in that it is not a chronically administered therapy, it sometimes needs to be repeated more than twice, and self-injection issues may nevertheless affect adherence, and convenient and less burdensome delivery methods can enhance adherence to the appropriate regimens [42]. Adherence to therapy in children treated with growth hormone was greater using a needle-free device than when using a conventional injection technique (13.4% compared with 6%, respectively) [43].

In patients with diabetes, medication adherence improved significantly (from 62 to 69%) after conversion from manual insulin delivery to the use of an analogue pen device, with a significantly higher proportion of participants maintaining adherence after conversion compared with the proportion achieved before (54.6% versus 36.1%, respectively) [44]. Cobden *et al.* reported an increase in medication possession ratio (MPR) from 59 to 68% after conversion from vials/syringes to a pen device. MPR is a commonly used measure of adherence to medication, with an MPR of 80% usually quoted as representing optimal adherence [45].

Furthermore, a crossover study in patients with diabetes examined patient preferences towards a disposable insulin dose-delivery system in comparison with the standard vial/syringe system. Patients reported a significantly lower fear of injection with the disposable dose device [46]. Modifications to a prefilled insulin pen device have reduced the force of injections. When comparing the modified device with its predecessor, 76% of patients rated the new device as superior in terms of simplicity and comfort [47].

The evolution of injection devices for MS therapy has led to some improvements in injection tolerability and patient satisfaction. Examples from other therapy areas suggest that these devices may well directly and indirectly enhance adherence to MS therapy. It is hoped that further refinements to MS injection devices will translate into greater patient satisfaction and motivation to remain adherent to therapy.

4.4 The new generation of injection devices in MS

The first electronic device for the injection of MS therapy has now been developed. The RebiSmart (RS; Merck Serono SA; Geneva, Switzerland) electronic auto-injector device, which uses multidose cartridges of the new formulation of s.c. IFN-β_{1a}, represents the most recent advance in injection technology for MS. The device automatically recognises contact with the patient's skin, encouraging correct injection, and delivers a controlled, pre-set dose of drug. It can be programmed with the following, adjustable, injection comfort parameters: injection depth, needle-insertion speed, medication-injection speed, and time that the needle remains in the skin after the injection is complete. The needle is hidden before and after injection, and it is hoped that this feature, in combination with the convenience and the adjustable injection comfort settings provided by this device, will further motivate patients to inject their IFN-β_{1a} treatment. The fact that the needle is hidden during the injection process, and therefore not accessible, decreases the likelihood of patient injury through mishandling the needle. Also, the device can be programmed to deliver various doses of IFN-β_{1a}. This feature is useful for dose titration at treatment initiation to minimise adverse events, and allows controlled dose reduction in patients who experience adverse events such as grade 3 hepatic or haematological toxicity.

The RS device can record the patient's dose history, allowing the physician to monitor the patient's adherence to therapy. This feature may also be useful for patients with memory or attention impairment, as the dosing log display serves as a reminder of when the patient last injected, making correctly timed self-administration easier. For more compromised patients these features may be helpful to caregivers, avoiding the risk of inappropriate (duplicated, more than omitted) injections. The information stored in the RS memory can also be entered into the iMED system, an electronic chart that enables physicians to monitor all aspects of disease and treatment in patients with MS. Also, this information can be made available to a wider database containing information on many patients. This feature of the RS may, in time, prove to supply valuable data on adherence to MS therapy.

A multi-centre, open-label, 12-week, Phase IIIb study is now underway to evaluate the suitability of the RS device in patients with MS. The primary outcome (to be measured at the end of the treatment period) is the proportion of participants rating the suitability of the device as 'very suitable' or 'suitable' for self-injecting. The secondary outcome measures are the incidence of predefined injection-site reactions, MSTCQ scores, side effects, McGill pain questionnaire responses, visual analogue scale results and ratings of injection pain.

5. Expert opinion

Poor adherence to medication regimens can lead to poorer outcomes for patients, and usually occurs as a consequence of several factors. Although oral drugs may soon be available as a treatment option for MS, for certain patients an injectable drug may be the only appropriate agent. To maximise adherence, patients with MS should be educated about the nature of their disease, with emphasis on the variable and unpredictable nature of MS. Patients benefit from the provision of information on what treatment may or may not achieve, as well as what to expect in terms of potential adverse events. Support strategies are important in maintaining patients' motivation to continue following the prescribed DMD regimen.

As the data presented above show, drug-delivery devices have the potential to address several factors related to adherence, and improved technical and mechanical properties of these devices have already increased the acceptability and ease of administration of therapy. The incorporation of new technology into the design of injection devices over the next few years is likely to assist in moving towards the important goal of optimal levels of adherence to injected MS therapies.

Further studies are required to determine whether the use of new, relatively sophisticated, delivery devices translates into better long-term adherence in patients with MS. The use of such devices may further improve injection tolerability and ease of administration, and may contribute to maintaining patient adherence to therapy.

The author's experience with the prototype of RS in the recently completed Phase IIIb study has been very positive: patients found it easy to use and helpful in increasing their independence and confidence; they also found the 30G needle very acceptable for injections in areas where the subcutaneous tissue is very thin and where injection can be painful. The indication to inject almost immediately instead of letting the solution reach room temperature was also appreciated, requiring less 'premeditation', and there was no apparent increase in the incidence of local side effects. Accurate and unobtrusive methods for measuring adherence in MS would be beneficial in optimising the outcomes of therapy. The dosing log feature of electronic injection devices may provide valuable information in this respect.

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