Research Article

Reviewing Medication Non-Adherence in Patients of Inflammatory Bowel Disease

Rashi Chauhan[1], Sarita Jangra Bhyan[2], Richa Chaudhary[1], Mukul Vishnoi[3], Sharad Kumar[1], Haider Imran[3]
1. Pharm D (Post Baccalaureate) Intern, 2. Internship Coordinator, Assistant Professor, 3. Pharm D Intern,
Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, TMU, Moradabad, Uttar Pradesh, India.
***Corresponding author's E-mail:** chauhan.rash1994@gmail.com

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which clinically contains Crohn's disease, ulcerative colitis, and other conditions. IBD has been considered one of the most prevalent gastrointestinal diseases with accelerating incidence in newly industrialized countries. Non-adherence negatively affects the efficacy, safety and costs of therapies. Non-adherence is a multifactorial problem. This systematic review (SR) of SRs (overview) aims to identify factors that can influence the adherence of adult patients with chronic physical diseases. Non-adherence to medication for individuals with IBD is estimated to occur in 65%-90% of adolescents and 55%-75% of adults. There appears to be a greater focus on unintentional adherence in adolescents compared with adults and more promising interactions. Routine clinical practice needs to be incorporated for new strategies to improve adherence in IBD patients.

Keywords: Inflammatory bowel disease, gastrointestinal tract, medications.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, which clinically contains Crohn's disease, ulcerative colitis, and other conditions. The inflammation of the intestinal mucosa in IBD is characterized by episodes of abdominal pain, diarrhea, bloody stools, weight loss, and the influx of neutrophils and macrophages that produce cytokines, proteolytic enzymes, and free radicals that result in inflammation and ulceration [1].

The pathogenesis of inflammatory bowel disease (IBD) is still unclear but in all probability is multifactorial and driven by an exaggerated immune response towards gut micro biome in a genetically susceptible host. Increasing evidence suggests that intestinal permeability may be crucial and some authors even considered IBD as an impaired barrier disease [2].

According to WHO medication adherence is defined as the extent to which a person's behavior in taking medications corresponds with agreed recommendations from a health care provider. In simple words medication adherence is defined as taking medication as prescribed for the proposed duration [3].

Non-adherence to medication can be defined as, 'a failure by patients to undertake activities or follow treatment recommendations made by health service providers'.

Prevalence Rate of IBD

The incidence and prevalence of IBD markedly increased over the second half of the 20th century, and since the beginning of the 21st century, IBD has been considered one of the most prevalent gastrointestinal diseases with accelerating incidence in newly industrialized countries. The highest prevalence of IBD was reported in Europe (ulcerative colitis 505 per 100,000 persons in the southeast of Norway; Crohn's disease 322 per 100,000 persons in Hesse, Germany) and North America (ulcerative colitis 286.3 per 100,000 persons in Olmsted County, USA; Crohn's disease 318.5 per 100,000 persons in Nova Scotia, Canada). The prevalence of IBD is increasing worldwide, with the result that ageing of the population makes IBD in the elderly a growing problem. Recent estimations indicate that approximately 20% of the United States (US) population will be aged >65 years by the year 2030.2 At present, 10–15% of patients diagnosed with IBD are aged >60 years.3 Of these, 65% present in their 60s, 25% in their 70s and 10% in their 80s. Since 1990, the incidence rate of IBD in Western countries was shown to be stable or started to drop, but the incidence rate in newly industrialized countries of Asia, Africa, and South America was increasing[4].

Epidemiology

Currently, there is no accepted universal definition of the term "elderly." Although "elderly" is often defined as those with chronological age 65 years or older in most developed countries, there is still some discrepancy in terms of the threshold value from a healthcare perspective, given that other markers of old age, such as the general health state or the presence of concomitant diseases, may influence the physical mark of old age. Previously published reviews on IBD in the elderly have set a threshold value of 60 years of age, whereas the age of 65 years has been fixed as a reference value for the definition of elderly in other report. Irrespective of the definition, the incidence and prevalence of IBD in the elderly are on the rise as a consequence of the ageing population. The evidence that IBD has relatively

little effect on lifespan further contributes to the increase in the number of individuals aged >65 years living with IBD. This increasing trend is more evident in high income than in low-income countries, but the process of urbanization, improved diagnostic methods and disease awareness have contributed to an increased IBD prevalence and incidence in regions such as Asia and the Middle East. Thus, it is expected that the increase in the incidence of IBD diagnosed in advanced age will continue to further increase in the next decades on a worldwide basis. Despite some variability of data across epidemiological studies due to regional differences and methods of diagnosis, the incidence rates of ulcerative colitis (UC) in the elderly are higher than those for Crohn's disease (CD) and range from 1 to 20/100,000 for UC in Europe and in the United States compared to 1 to 10/100,000 for CD in Europe. A recently published National cohort study in Sweden has reported that 23% of subjects with diagnosed IBD had a first diagnosis of IBD at age ≥60 years and that in elderly patients, the IBD incident rate was 35/100,000 person/years (male: 37; female: 33) and was 10/100,000 for CD, 19/100,000 for UC, and 5/100,000 for IBD unclassified. Irrespective of the age at diagnosis, epidemiological studies have estimated that about 25–35% of individuals with IBD are >60 years of age [5].

Non-Adherence

Intentional medication non-adherence – "Active process whereby the patient chooses to deviate from the treatment regimen."

Unintentional medication non-adherence – "Passive process in which the patient may be careless or forgetful about adhering to treatment regimen."

Non-adherence negatively affects the efficacy, safety and costs of therapies. Non-adherence is a multifactorial problem. This systematic review (SR) of SRs (overview) aims to identify factors that can influence the adherence of adult patients with chronic physical diseases. Non-adherence can be *intentional* when the patient personally decides not to adhere to a cure program or *accidental* when the intention to adhere is conserved but some practical issues interfere with adherence, such as forgetfulness. It's also important to specify that adherence is generally superior in patients with acute vs chronic conditions requiring long-term therapies and periodic medical appointments: in these patients, progressive reduction in therapy assumption has been described after 6 months from starting therapy. We should also consider that the management of any chronic disease is related to the concept of *self-management* which includes multiple domains, unique to each patient, rather than involving the healthcare provider–patient relationship, or the social environment where the patient's lives in [6].

Patient Types

Patients can be sub-categorized into four main types according to their adherence behaviour towards prescribed medication: gamblers, teacher's pets, rebels and distractible. Gamblers are aware of the potential benefits of medication but often take a chance that they will come to no harm if medication is missed, akin to smokers who take a chance that they will avoid cancer. An example that clearly illustrates this is in the case of statin therapy. Despite good evidence showing that continued statin therapy over 5 years can save approximately one life in 20 patients who previously suffered a myocardial infarction, 12 more than half of the patients stop taking their medications after about 2 years.13 Those patients who fall within the category of 'teacher's pets' are likely to do what their physician asks them to do, whereas 'rebels' will do the exact opposite of what is requested. The fourth category of patients are classed as 'distractible', primarily because they are often pre-occupied and forget to do the things they have been asked [7].

Determinants of Adherence to Medication

A range of determinants were extracted based on the source publications. These were further categorized according to their effect on adherence to medication using an adherence determinant matrix. Relevant dimensions included:

- Treatment duration: long- vs. short-term treatment;
- Components of adherence to medication: implementation of the dosing regimen (defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) vs. persistence (defined as the length of time between initiation and the last dose which immediately precedes discontinuation). Determinants were categorized under implementation unless original review wording clearly addressed persistence.
- Dimensions of adherence: these were socio-economic factors, healthcare team- and system-related factors, condition-related factors, therapy-related factors, and patient-related factors, demographic variables were included under patient-related, instead of socio-economic related factors.
- Direction of effect: determinants were classified according to their positive, negative, neutral, or not defined effect on adherence [8].

METHODS

A review of articles was done to examine adherence data in inflammatory bowel disease. A total of 41 articles were collected from google scholar of last ten years on non-adherence and its comparison in different age groups of patients.

DISCUSSION

Non-Adherence is a common issue amongst people diseased with IBD. Yet identification of non-adherence is the vital first step in attempting to avoid the increased health burden for the patient and financial burden for the healthcare system associated with non-adherence. As with

precious studies, we found that distress in IBD patients was associated with impaired health related quality of life .

According to **Kartik ashok et al.(2017)[3]** conducted a study which they determined medication adherence. In the baseline visit, 6.36% patients had low adherence, 62.73% patients had medium adherence, 30.91% patients had high adherence. During follow up visit, 3.64% patients had low adherence, 18.18% patients had medium adherence and 78.18 % patients had high adherence. Busy/occupied (28.18%) was one of the main reasons for poor adherence followed by forgetfulness (20.91%), lifelong treatment (11.82%), side effects of drugs (11.82%), cost of medicine (10.90%), disease remission (8.18%), inconvenience (4.55%), and multiple daily dosing (3.64%)[3].

D'inca et al. (2008)[6] found that patients with a longer diagnosis (≥5 years; 15%) were more likely to be adherent than patients with a shorter diagnosis (<5 years; 24%)[6].

Knight-Reed Bonney (2010)[16] and et al in their study showed Adolescent-reporting Adherence to Prescription and OTC Medications, For adolescent reported adherence to prescription medications, time since diagnosis (p ¼ .02), adolescent perceived disease severity (p ¼ .05), and the adolescent's a motivation to adhere to the medication regimen (p ¼ .02) emerged as significant predictors. Adolescents who had been diagnosed for fewer months and reported less disease severity and a motivation reported better adherence to prescription medications & Adolescent-reported Adherence to OTC Medications Based on adolescents' reports of adherence to OTC medications, time since diagnosis emerged as a significant predictor (p < .01), with adolescents who had been diagnosed longer reporting poorer adherence. Parent Report of Adherence to Prescription Medications In the final model predicting parent report of adherence to prescription medications, no significant predictors were identified. And further Parents Report of Adherence to OTC Medications established that Significant predictors of parent-reported adherence to OTC medications were time since diagnosis (p ¼ .02), parent-perceived disease severity (p ¼ .01), parent-reported maternal involvement (p < .01), and parent report of the frequency of parent–adolescent conflict (p < .001). Parents who reported less time since diagnosis, greater perceived disease severity, more maternal involvement in the management of their adolescent's IBD, and less parent– adolescent conflict reported greater adherence[16]. According to **Simon R. Knowles (2012)**[17] rates of adherence were found to be adolescents tend to be approximately 10%–20% more adherent, with this observation being more pronounced in early adolescence. Adults can be slower to develop good medication adherence. In contrast, adolescents tend to become less adherent over time if they are not supported to establish good adherence habits early. And there are some promising impacts found of non-adherence Trindade, Ehrlich, Kornbluth, and Ullman (2011) found that low adherers were significantly more likely to report higher disease activity. This is evidenced by the findings of Taft, Keefer, Leonhard, and Nealon-Woods (2009), which found social stigma to account for 5% of the variance in adherence to medication, after controlling for demographic variables and illness characteristics (e.g., remission status, flare ups, flare-up duration). Similarly, qualitative findings suggest the social embarrassment of taking multiple pills and fatigue of long-term medication use are potential barriers to. Research by Horne et al. (2009) examined IBD patient attitudes regarding maintenance therapy and found attitudes of skepticism (*low* perceived need, *high* concerns), indifference (*low* need, *low* concerns), and ambivalence (*high* perceived need, *high* concerns) to predict nonadherence, independent of clinical and demographic factors. Struggles with mental health, such as anxiety (Nahon et al., 2011) and depression (Goodhand et al., 2013 ; Long et al., 2014; Nahon et al., 2012; Shale & Riley, 2003) also impact adherence. However, it should be noted that adult IBD patients report a range of different strategies to aid with adherence, including using daily routine as cues (78%), a medication dispenser (17%), calendar or checklist (6%), reminder from a family member (6%), and blister pack from the pharmacy (3%; Ediger et al., 2007). A study by Nguyen et al. (2009) of 235 IBD patients found that greater trust in their physician was associated with a decrease in nonadherence, and for each half a standard deviation increase of trust, there was a 41% increase in odds of being adherent. Similarly, having a negative relationship with medical professionals is associated with over a five-fold risk of low adherence (Mountifield et al., 2014). Tae et al. (2016) found that low medication knowledge is associated with a 5.6-fold increased risk of nonadherence. After taking into account potential confounders and nonadherence risk factors, Pittet et al. (2014) found active information-seeking patients

or just being careless at times about taking medication (12%–38%; López San Román et al., 2005; Sewitch et al., 2003). In contrast, intentional reduce-dose nonadherence is self-reported as being due to feeling well and no need to continue (11%–64%; Cˇ ervený, Bortlík, Kubeˇ na, et al., 2007 ; Cˇ ervený, Bortlik, Vlcek, et al., 2007 ; Ediger et al., 2007 ; López San Román et al., 2005; Sewitch et al., 2003), adverse side effects (9%–33%; Cˇ ervený, Bortlík, Kubeˇ na, et al., 2007; Cˇ ervený, Bortlik, Vlcek, et al., 2007; Ediger et al., 2007; López San Román et al., 2005 Sewitch et al., 2003), reducing dose by oneself without the doctor (11%–32%; Ediger et al., 2007; Horne et al., 2009), reducing the dose to avoid running out before appointment (18%–22%; Cˇ ervený, Bortlík, Kubeˇ na, et al., 2007; Cˇ ervený, Bortlik, Vlcek, et al., 2007), reduce dose to reduce medication costs (25%; Ediger et al., 2007), deciding to skip doses (17%; Horne et al., 2009), not refilling their prescription in time (11%–15%; Cˇ ervený, Bortlík, Kubeˇ na, et al., 2007; Cˇ ervený, Bortlik, Vlcek, et al., 2007), unpleasant associations with medication (13%; Ediger et al., 2007), uncertainties about the effectiveness of medication (12%;Ediger et al., 2007), or pregnancy or breastfeeding in women (4%–10%; Cˇ ervený, Bortlik, Vlcek, et al., 2007). Regarding increase-

dose intentional nonadherence (i.e., self-medicating), self-reported reasons include suspected worsening of disease (80%; Bernal et al., 2006), fear of hospitalization (12%; Bernal et al., 2006), and fear of being on sick leave (10%; Bernal et al., 2006).And in Adolescent IBD Cohorts Unintentional nonadherence in adolescents is often referred to as barriers to adherence (e.g., forgetting; Hommel & Baldassano, 2010). Semistructured clinical interviews (Medication Adherence Measure [MAM]; Zelikovsky & Schast, 2008), which assess perceived barriers to medication adherence (e.g., "Ran out/didn't fill," "Not feeling well"), reveal that adolescents with IBD report an average of 2.6–2.9 distinct barriers to adherence (Hommel, Denson, & Baldassano, 2011 ; Ingerski, Baldassano, Denson, & Hommel, 2010). Commonly reported barriers include forgetting (85%– 94%; Gray, Denson, Baldassano, & Hommel, 2012 ; Hommel & Baldassano, 2010), not being home (43%–75%; Gray et al., 2012 ; Hommel & Baldassano, 2010), medication interfering with an activity (34%– 69%; Gray et al., 2012 ; Hommel & Baldassano, 2010), regimen complexity (63%; Hommel & Baldassano, 2010), difficulty swallowing pills (56%; Hommel & Baldassano, 2010), and running out due to not refilling a prescription in time (15%; Gray et al., 2012). The time of day can also act as a barrier, and adolescents are least likely to miss a dose during lunchtime at school (10%) and dinner time (12%; Ingerski et al., 2010). Barriers to adherence have also been found to interact with other predictors. As noted above in Gray et al. (2012) , anxiety/depressive symptoms moderate the barriers–adherence relationship, with high anxiety/depression adolescents reporting poorer adherence in relation to barriers, compared with low anxiety/depression adolescents. Barriers to adherence have also been shown to mediate the relationship between both attention problems and conduct problems with parent-reported adherence, underscoring the potential significance of behavioral functioning in identifying youth at-risk of nonadherence (Reed-Knight et al., 2013). Peer victimization is associated with lower adherence, and prosocial support moderates its impact (Janicke et al., 2009). As such, several publications have recommended the development of problem-solving skills among adolescents with IBD as a means of maneuvering barriers and optimizing adherence (Greenley, Gumidyala, et al., 2015 ; Hommel, Denson, et al., 2011 ; Hommel et al., 2012). Knowledge about medication also affects adherence. Greenley, Stephens, et al. (2013) assessed the level of knowledge regarding nutritional supplements in IBD among 68 adolescent IBD patients. Comparing those who did not know and those who knew specifically how a multivitamin helped them, a large effect size was found on adherence with those having specific knowledge of the medication. In a sample of 100 adolescent IBD patients, Schurman et al. (2011) found that the rate of unintentional nonadherence (73%) was higher than intentional (35%), and that the two kinds of nonadherence were not significantly correlated. Intentional nonadherence predicted 8%–10% additional variance in disease severity beyond age and gender alone. The approach to risk factors for poor adherence differs between adults and adolescents. In adults, the emphasis is placed upon developing a positive and trusting physician–patient relationship, rather than demographic factors. Most frequently, when nonadherence occurs, it is unintentional and less-well integrated with the patient's routine. For adolescents, the terminology for unintentional nonadherence is barriers (e.g., Hommel & Baldassano, 2010)[17].

And as a study conducted by **Anisa Soobraty and et al (2017)[22]** they stated that approximately half of respondents had 15 years' experience or more. Of the 68 medically qualified respondents 32 classed themselves as general gastroenterologists, 18 had an IBD interest and 18 stated that they were IBD experts. The number of patients seen in an average week varied greatly amongst the study's participants between less 10 to over 100 patients with a mean of 25 patients per week. Non-adherence in their local patient cohort was perceived as a frequent problem by 43%, as an infrequent problem by 49%, while 7% reported few cases only and 1% reported no adherence issues Perceived reasons for non-adherence[22].

CONCLUSION

Adherence to treatment in IBD patients is a significant factor in predicting disease relapse, and is associated with an increased risk of long-term colorectal cancer. During the past few decades, the prevalence of IBD has mainly increased gradually among elderly people. A growing number of patients with IBD onset in adults are living past the age of 60. The rising global incidence of IBD and an aging population means that the prevalence of IBD among elderly people is likely to increase. Most studies reported that non-adherence can be as high as 45% the main reason being both intentional and accidental or sometimes related to patient's belief about the disease and its treatment .Non-adherence to medication for individuals with IBD is estimated to occur in 65%-90% of adolescents and 55%-75% of adults. There appears to be a greater focus on unintentional adherence in adolescents compared with adults and more promising interactions. In general, the treatment of IBD in the elderly is similar to that administered to younger patients, with a few relevant exception must be made between fit elderly and frail elderly. The former should not be excluded from newer therapy or clinical trials simply because of age. The risk of non-adherence is increased by polypharmacy which is very common among elderly patients and complex regimens. Once daily dosing can improve adherence, particularly in patients with older IBDs. Compared with general population, older patients diagnosed with CD are at higher risk for several types of cancer increased age is an independent risk factor for mortality among IBD patients. Non-adherence is a significant problem in the management of IBD, which could lead to adverse clinical outcomes including an increase in disease activity relapse, high morbidity & mortality, increased health expenditure, disability and possibly poor quality of life. Although less is

spent on medication when one is non-adherent, the cost of complication associated with non-adherence on the healthcare system is significantly higher. To promote adherence with treatment in patients is a challenging task for healthcare providers. Routine clinical practice needs to be incorporated for new strategies to improve adherence in IBD patients. Now more than ever as we face high costs of the new and more expensive drugs with adverse effects occasionally. IBD treatment has changed with spread use of biologic therapies, which may reduce patient burden. Hence healthcare providers should help patients with IBD by establishing good communication, information, simple regimen, overcoming barriers, focusing on modifiable & multimethod evaluation. Various interventions exist, such as education dose implication, use of audio-visual reminder systems and multi-factored approach can be proved efficacious to improve adherence. Evaluating external variables that could be associated with adherence, such as assumptions about the efficacy of prescription and OTC drugs, as well as longitudinally evaluating adherence to identify significant predictors of adherence through the developmental period. This would also be relevant for young people diagnosed with IBD to determine the correlation between barriers and adherence to both prescription and OTC medications. Identifying unique predictors for adherence to medicines will be important for health care professionals working to improve adherence in patients diagnosed with IBD and to develop manualized interventions for adherence promotion in the future.

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