Dynamics of Patient-Based Benefit-Risk Assessment of Medicines in Chronic Diseases: A Systematic Review

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Background: A critical gap exists in understanding the dynamics of patient-based benefit-risk assessment (BRA) of medicines in chronic diseases during the disease journey.

Purpose: To systematically review and synthesize current evidence on the changes of patients’ preferences about the benefits and risks of medicines during their disease journey including the influence of disease duration and severity, and previous treatment experience.

Methods: A systematic review of studies identified in PubMed and Embase, from inception to November 2020, was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Articles were eligible if they analyzed adult patient-based BRA of medicines with a chronic disease, based on at least one of the pre-specified dimensions: disease severity, disease duration, or previous treatment experience.

Results: A total of 26,228 articles were identified and 105 were eligible for inclusion. Of these, 85 detected a variation in patient-based BRA of medicines with at least one of the pre-specified criteria. Patients with higher disease severity and more treatment experience have increased risk tolerance. It remains inconclusive whether disease duration directly affects the relative importance of a patient’s preference.

Conclusion: Factors important for patients’ BRA of their medicines during a chronic disease journey vary more with their clinical situation and previous treatment experience than with time since diagnosis. Due to the importance of these factors on patients’ perspectives and potential impact on their decision-making and eventually their clinical outcomes, there is a need for more studies to assess the dynamics of patients’ BRA in every disease.

Keywords: patient preference, choice behavior, decision making, health knowledge, attitudes, practice, attributes, risk tolerance

Introduction

Benefit-risk assessment of medicines (BRA) is primarily an exercise that balances two dimensions: the dimension of benefit which includes not only therapeutic efficacy but also improvement of quality of life, and the dimension of risk which consists of the safety profile of the given medicine and the potential risk of unobserved adverse events anticipated on the basis of the mechanism of action and mode of administration. The dimension of cost is also often embedded in this analysis. BRA of medicines – based on current evidence – is regularly performed at multiple levels to ensure the judicious and safe use of medicines: at a macro-level in regulatory decisions, at a meso-level in guidelines setting, and at a micro-level in shared-decision making. Often, however, expert assessment fails to incorporate patients’ preferences and perceptions that might be incongruous with clinicians’ presumptions and opinions. A patient-based BRA can...
complement the expert evidence-based analysis and therefore enhance patients’ involvement, satisfaction, and ultimately adherence, and clinical outcomes. The concept of a more patient-focused evaluation of medicines has emerged and has gained increasing attention from experts and researchers in the last decade. Patient-based BRA of medicines is commonly associated with sociodemographic characteristics but it is unclear if an individual’s patient-based BRA changes during disease progression. Evidence shows that patients tend to evaluate the benefits and risks of their medicines on a shorter time scale than medical professionals. However, they may continue to revise their initial BRA and expectations as a result of eventual iterative trial and evaluation, experiences with unwanted side effects, and improvement or worsening of their condition. Increasing numbers of consecutive treatments and a longer disease duration result in an “experienced patient” and in the setting of a chronic disease this may well influence treatment preferences and benefit risk trade-offs.

Little is known about the dynamics of patient-based BRA of medicines during chronic disease journeys. We therefore aim to systematically review current evidence on the changes of patients’ preferences about the benefits and risks of their medicines during their disease journey, specifically with longer disease duration, increased disease severity, and treatment experience.

Methods
We developed a protocol for our review (PROSPERO ID: CRD42020190966) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Systematic Literature Search
We performed a systematic search using PubMed and EMBASE databases from inception to 30 November 2020 using a validated generic search strategy to retrieve published data on patient-based BRA of medicines, in combination with search terms relevant to chronic diseases and corresponding treatments. We provided the search syntaxes used in PubMed and EMBASE in Supplementary Information 1. We included studies if they analyzed perceptions or preferences of adult patients (>18 years) with a chronic disease about the balance of benefits and risks of their treatment based on stage of the disease, treatment history, other clinical characteristics, or time post-diagnosis. Chronic diseases, also known as noncommunicable diseases, tend to be long lasting conditions with persistent effects. They are generally the result of a combination of genetic, physiological, environmental and behavioral factors. The most reported chronic conditions groups include arthritis, asthma, back pain, cancer, cardiovascular disease, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, mental health conditions and osteoporosis.

We excluded studies if they predominately discussed adherence, failed to address patients’ perceptions or preferences on the benefits and risks of chronic treatment, addressed public perceptions or preferences on the benefits and risks of preventive treatment, or did not have a sub-group analysis of patient preferences based on at least one of three pre-specified dimensions: disease severity, disease duration and previous treatment experience. We chose these dimensions as indicators of disease progression in chronic conditions. In fact, long-standing disease duration is a hallmark of chronic conditions. Moreover, adapting therapeutic strategies based on disease severity and previous lines of treatment is an overarching principle in the management of chronic diseases.

Data Extraction
Two reviewers (HM and SH) fully reviewed and independently assessed studies for inclusion and extracted data into a spreadsheet. We resolved disagreements by discussion and adjudication with a third reviewer. For each article that met our inclusion criteria, the two reviewers independently extracted the data. We collected information relevant to the STROBE checklist and specifically included: authors, year of publication, study country, disease or condition, sample size, target study population plus age and gender, methods used to elicit patient preferences, attributes assessed, and summary of findings.

Quality Assessment
There are no established criteria to assess risk of bias or the methodological quality of patient preference studies but some reviewers have adapted existing quality assessment models used for randomized clinical trials or constructed a new
We adopted a checklist constructed by Eiring et al\textsuperscript{16,17} consisting of 31 quality criteria within five domains: 1) external validity of the study, 2) quality of construct representation, 3) minimization of the risk of construct-irrelevant variance due to multiple factors such as impairments in the cognitive abilities of the participants, numeracy skills, emotions and prejudices, 4) quality of reporting and analysis, and 5) other aspects that may strengthen or weaken the study. Two reviewers (HM and SH) independently scored all studies and categorized them into high, medium, and low overall quality, with disagreements resolved by consensus (Supplementary Information 2, Table S1).

Data Synthesis and Analysis
A meta-analysis was not appropriate because the included studies would be methodologically and clinically diverse. Therefore, we qualitatively synthesized the results and presented them in narrative and tabular forms to clarify the nature of changes patient-based BRA of medicines with longer disease duration, increased disease severity, and more patient treatment experience. We used our findings to develop a model of the interrelationships and dynamics of patient-based BRA of medicines in chronic disease.

Results
The search returned 26,228 records and we removed 955 duplicate records (using automatic deduplication in Endnote followed by a manual process). We screened the 25,273 remaining articles at title and abstract level; 544 articles were assessed for inclusion. After full text review, 105 eligible articles were included (Figure 1).

![Figure 1 Flowchart of literature search results.](https://doi.org/10.2147/PPA.S375062)
Study Characteristics

These articles assessed the variation of patient-based BRA of medicines with at least one of three pre-defined criteria for this systematic review: disease duration, disease severity, and treatment experience. Most articles (n = 78, 74%) investigated the variation of patient-based BRA of medicines with one of these dimensions, 26 articles (25%) investigated the variation of patient preferences with two dimensions; only one article (1%) examined all three (Table 1). Four in five studies (n = 85, 81%) detected a variation in patient-based BRA of medicines with at least one of the three pre-specified dimensions. There was no association between any of the three dimensions and patient preferences of medicines attributes in 20 studies (19%).

Most articles (n = 79, 75%) were published between 2010 and 2020, a quarter (n = 25, 24%) between 2000 and 2009, and one article (1%) was published before 2000. Predominately, the studies were conducted in one country (n = 87, 83%), with the majority from North America and Europe. There was a wide range of therapeutic areas, including autoimmune, cardiovascular, and gastrointestinal diseases, diabetes, and cancer (Table 1). All studies conducted their analyses at a specific point of time of the chronic condition, and there were no studies taking multiple BRA measures over an extended period.

68% (n = 71) of studies were of medium quality, 24% (n = 25) were high, and 8% (n = 9) were of low quality (Supplementary Information 1). High-quality studies typically had a detailed and efficient process to construct attributes and levels, as well as a high effort to minimize the risk of irrelevant variance, by piloting the study or sequencing the questions. 95% of studies were rated high in the quality of reporting and analysis, particularly for the analysis of pre-specified measures and patients’ subgroups.

The number of participants in the included studies varied between 11 and 14,033 and two-thirds of the studies (n = 66, 63%) had between 101 and 500 participants with eight studies (7%) including more than 1000 participants (Table 1). Participants were predominantly female with 35 studies having less than 50% female participants. In most studies (94%) the targeted population were outpatients; only three studies had a mixed cohort of inpatients and outpatients, and three studies did not report these details. There were many recruitment approaches and settings, and some studies adopted more than one approach to achieve the targeted sample size and ensure a representative group of patients. The approaches encompassed recruitment via patient and consumer panels, research agencies, patient registries and databases, patient societies and local groups, and in clinics, specialty centres, and hospitals. Almost half of the studies (n = 50, 48%) reported the response rate, which varied between 7% and 100%.

All studies included a well-defined study question and conducted pre-specified analyses; 22 studies (21%) combined two or more methodologies (Table 1). The analyses were predominantly quantitative; only two studies were qualitative and eight had a mixed method approach. The strategies to elicit patient preferences for their treatment attributes included: discrete choice experiment, other conjoint analysis method, standard gamble, time trade-off, willingness to pay, best-worst scenario, survey or questionnaire, interview, and other methods. The attributes most frequently investigated were outcome-related attributes (n = 98, 93%), mainly efficacy and safety, as well as process-related attributes (n = 68, 65%), including mode of administration and frequency and timing of dosage. Cost-related attributes were assessed in 34 studies (32%).

Disease Duration

Twenty-three studies (22% of total included studies) addressed the variation of patient-based BRA of medicines with disease duration (Table 2): 8 studies (35% of subset) found that with a longer disease duration, patients tend to accept a higher risk of potential side effects and/or higher cost in trade of higher efficacy whereas three studies (13% of subset) reported the opposite. Twelve studies (52% of subset) did not detect any variation in patient preferences with disease duration.

Disease Severity

Fifty-one studies (49% of total included studies) measured the impact of disease severity on patient-based BRA of medicines (Table 3). Overall, 29 studies (57% of subset) reported patients were more willing to accept a higher risk of treatment-related side effects or a higher cost of treatment when they had more severe symptoms, more disease damage, or a higher risk for disease progression. Thirteen studies (25% of subset) reported a greater risk aversion and a reduced importance for efficacy with disease progression whilst the reminder (n = 9, 17% of subset) found no variation of patient-based BRA with disease severity.
Table 1 Description of Studies Included in the Systematic Review

| Aspect and Categories                                      | n  |
|------------------------------------------------------------|----|
| Year of publication                                        |    |
| Before 2000                                                | 1  |
| Between 2000 and 2009                                      | 25 |
| Between 2010 and November 2020                            | 79 |
| Number of participants                                     |    |
| ≤100                                                       | 14 |
| 101–500                                                    | 66 |
| 501–1000                                                   | 17 |
| >1000                                                      | 8  |
| Females in the study population (%)                        |    |
| <50%                                                       | 35 |
| 50–75%                                                     | 38 |
| >75%                                                       | 32 |
| Response rate (%)                                          |    |
| <25%                                                       | 5  |
| 25–49%                                                     | 10 |
| 50–74%                                                     | 16 |
| ≥75%                                                       | 19 |
| Not reported                                               | 55 |
| Analysis approach                                          |    |
| Quantitative analysis                                      | 95 |
| Qualitative analysis                                       | 2  |
| Mixed-methods approach                                     | 8  |
| Methods used for patient preferences elicitation          |    |
| Discrete choice experiment                                 | 47 |
| Conjoint analysis (other than discrete choice experiment) | 18 |
| Standard gamble                                            | 5  |
| Time trade-off                                             | 6  |
| Willingness-to-pay                                         | 10 |
| Best-worst scenario                                        | 3  |
| Toxicity trade-off                                         | 1  |
| Probability discounting                                    | 1  |
| Threshold questions                                        | 1  |
| Decision-making questionnaire                              | 1  |
| Multicriteria decision analysis                            | 1  |
| Maximum difference scaling                                 | 1  |
| Rating scale                                               | 1  |
| Forced ranking                                             | 1  |
| Survey or questionnaire                                    | 27 |
| Interview                                                  | 7  |
| Focus group                                                | 1  |
| Attributes studied                                         |    |
| Outcome-related attributes                                 | 98 |
| Efficacy                                                   | 90 |
| Safety                                                     | 92 |
| Quality of life                                            | 9  |
| Process-related attributes                                 | 68 |
| Mode of administration                                     | 47 |

(Continued)
**Table 1 (Continued).**

| Aspect and Categories                          | n  |
|-----------------------------------------------|----|
| Frequency and timing of dosage                | 52 |
| Device-related and storage properties         |  8 |
| Waiting time for medicine administration      |  4 |
| Location of administration                    | 15 |
| Cost-related attributes                       | 34 |

**Table 2 Studies Assessing the Variations of Patient-Based BRA of Medicines with Disease Duration**

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results                                                                 |
|-------------------------------|-----------|-----------------------------------------------|-------------|----------------------|----------------------------------------------------------------------------------|
| Aristides et al 2004          | France, Germany, Italy, Spain, and the United Kingdom | Discrete choice conjoint analysis, Recruitment by a research agency | 290         | Type 2 Diabetes mellitus | The longer a patient had had diabetes, the greater the willingness to pay for treatment |
| Arroyo et al 2017             | Spain     | Conjoint analysis, Recruitment by treating neurologists | 221         | Relapsing-remitting multiple sclerosis | Patients with a recent diagnosis (<1 year) had the highest importance assigned to side effect risk |
| Bauer et al 2020              | Australia, Canada, Germany, Switzerland and the United States | Discrete choice exercise, Recruitment through local patient groups | 485         | Relapsing-remitting multiple sclerosis | Patients diagnosed <10 years ago were more concerned about the safety profile of the therapy, while patients diagnosed ≥10 years ago place most importance on treatment efficacy |
| Garcia-Dominguez et al 2016   | Spain     | Discrete choice experiment, Recruitment by patient associations | 125         | Multiple sclerosis | Patients with shorter disease duration (less than 5 years) were significantly less concerned about preventing progression than those with 5 or more years since diagnosis, and more concerned about treatment side effects |
| Johnson et al 2007            | The United States | Conjoint analysis, Recruitment by an online panel and from clinical practice sites | 580         | Crohn’s disease | Patients who have been diagnosed for more years are willing to accept a higher risk of serious adverse events |
| Kromer et al 2015             | Germany   | Conjoint analysis, Recruitment from clinic | 200         | Psoriasis | With longer disease duration, sustainability of efficacy became increasingly more important for patients |
| Meads et al 2017              | The United Kingdom | Discrete choice experiment, willingness-to-pay, Recruitment from care centers | 221         | Pain management in cancer | Patients with longer disease period were more averse to severe pain than those with a more recent diagnosis, and required more efficacy from treatment |

(Continued)
Table 2 (Continued).

| Reference, Year of Publication | Countries          | Study Design and Recruitment of Participants                                                                 | Sample Size | Disease or Condition | Summary Results                                                                                                                                 |
|-------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------|-------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Morillas et al 2015<sup>37</sup> | Spain and Portugal | Discrete choice experiment, willingness-to-pay Recruitment from hospitals and clinics                          | 330         | Type 2 diabetes mellitus | Patients with longer disease duration put more importance on outcomes rather than convenience                                                 |
| Schaarschmidt et al 2011<sup>38</sup> | Germany            | Conjoint analysis Recruitment from a university medical center                                                | 163         | Psoriasis           | Patients with longer disease duration attached significantly greater importance to duration of benefit and less importance on side effects than those with shorter disease duration |
| Patients accepting less risk or cost with longer disease duration |                   |                                                                                                               |             |                     |                                                                                                                                                  |
| Manjunath et al 2012<sup>39</sup> | The United States  | Discrete choice experiment/conjoint analysis Recruitment from a patient panel                                 | 193         | Epilepsy            | Patients with a longer history of epilepsy were less likely to accept an add-on antiepileptic agent                                              |
| O’Brien et al 1990<sup>40</sup> | The United Kingdom | Questionnaire/ Standard gamble Recruitment from a specialized hospital                                         | 100         | Rheumatic diseases   | Patients who had been diseased for a greater number of years had less willingness to accept risk associated with treatment                         |
| Schaarschmidt et al 2018<sup>41</sup> | Germany            | Discrete choice experiment Recruitment in dermatology centres and via a patient organisation                  | 222         | Psoriasis           | With increasing disease duration, patients put less importance on efficacy and more importance on safety                                          |
| No variation of patient preferences with disease duration |                   |                                                                                                               |             |                     |                                                                                                                                                  |
| Bottomley et al 2017<sup>18</sup> | The United Kingdom | Discrete choice experiment Recruitment by a medical recruitment agency                                         | 350         | Multiple sclerosis  | No significant differences in preferences found in sub-group analysis based on time since diagnosis                                             |
| Bruce et al 2018<sup>19</sup> | The United States  | Questionnaire/ Probability discounting Recruitment from a specialty clinic and via a specialized patient newsletter | 225         | Relapsing-remitting multiple sclerosis | Discounting of efficacy or side effects did not significantly differ with diagnosis duration                                                   |
| Choi et al 2008<sup>20</sup>   | The United States  | Interview Recruitment from a clinic                                                                            | 52          | Asthma              | No differences found in patients’ perception of benefits or drawbacks of medicines according to disease duration                                  |
| Fraenkel et al 2001<sup>21</sup> | The United States  | Adaptive conjoint analysis Recruitment in community practices                                                  | 103         | Lupus nephritis     | No associations found between disease duration with patients’ preferences                                                                       |
| Gelhorn et al 2019<sup>22</sup> | The United States  | Discrete choice experiment/ Interview Recruitment from clinical sites                                         | 47          | Severe asthma       | Treatment preferences were similar regardless of years since diagnosis                                                                            |
### Table 2 (Continued).

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|------------------|
| Johnson et al 2009<sup>23</sup> | The United States | Discrete stated choice survey Recruitment from multiple patient panels | 651 | Multiple sclerosis | Maximum acceptable risk for serious adverse effects did not change with years of diagnosis |
| Lewis et al 2020<sup>24</sup> | The United Kingdom, The United States, and Germany | Discrete choice experiment Recruitment via recruitment agencies, patients support groups, and patient key opinion leaders | 450 | Chronic obstructive pulmonary disease | The time since diagnosis did not change the relative importance patients had put on their medicines’ attributes |
| Rigopoulos et al 2017<sup>25</sup> | Greece | Discrete choice experiment Recruitment from clinics | 310 | Psoriasis | Duration of the disease had no influence on patients’ treatment preferences |
| Scarpato et al 2010<sup>26</sup> | Italy | Questionnaire Recruitment from rheumatology centers | 822 | Rheumatoid arthritis | Patients’ preferences for route of administration were not influenced by disease duration |
| Tada et al 2019<sup>27</sup> | Japan | Discrete choice experiment Recruitment via a patient panel | 395 | Psoriasis | Disease duration had no impact on patients’ preferences |
| Turk et al 2020<sup>28</sup> | The United States | Discrete choice experiment/ Best-worst scenario Recruitment via patient panels | 602 | Osteoarthritis pain or chronic low back pain | No significant differences found in patients’ preferences based on time living with chronic pain |
| Wong et al 2013<sup>29</sup> | The United States | Discrete choice experiment Recruitment from a cancer center and a community hospital | 400 | Cancer | No association found between years of diagnosis and patient preferences |

### Table 3 Studies Assessing the Variations of Patient-Based BRA of Medicines with Disease Severity

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|------------------|
| Patients accepting higher risk or cost with higher disease severity |
| Alcusky et al 2017<sup>32</sup> | The United States | Discrete choice experiment Recruitment from consumer and patient panels | 196 | Psoriasis | With more severe symptoms, patients put more importance on efficacy. |
| Athavale et al 2018<sup>33</sup> | The United States | Discrete choice experiment Recruitment from an independent respondent panel | 514 | Treatment-naive overactive bladder | Respondents with nocturia put higher relative importance for treatments that reduced nocturia |
| Reference, Year of Publication | Countries          | Study Design and Recruitment of Participants | Sample Size | Disease or Condition       | Summary Results                                                                                                                                                                                                 |
|--------------------------------|-------------------|---------------------------------------------|-------------|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brooks et al 201944            | Japan             | Discrete choice experiment Recruitment by a patient recruitment organization | 161         | Type 2 Diabetes mellitus  | Patients with a higher HbA1c placed more significance on efficacy and HbA1c change                                                                                                                            |
| Bruce et al 201845             | The United States | Questionnaire Recruitment from a clinic, via letters, and via advertisements online and in a specialized patient newsletter | 290         | Multiple sclerosis        | Patients with more progressive disease reported increased willingness to take medications when confronted with possible severe side effects.                                                                       |
| Chapman et al 201446          | The United Kingdom| Questionnaire Recruitment from general practices | 398         | Epilepsy                  | Patients with more seizures have more positive perceptions about their medicines                                                                                                                                |
| de Bekker et al 200847         | The Netherlands   | Discrete choice experiment/ Trade-off Recruitment from general practices | 120         | Osteoporosis              | High-risk patients accepted a less effective drug to reduce their fracture risk                                                                                                                                  |
| Fayad et al 200848             | Lebanon           | Survey Recruitment by treating physicians in clinics and hospitals | 693         | Rheumatoid arthritis      | Radiographic damage was associated with a significant change in patients’ preferences                                                                                                                        |
| Fox et al 201549               | The United States | Standard gamble Recruitment from an online registry | 5446        | Multiple sclerosis        | Patients with an increased disability level had higher risk acceptance to therapies                                                                                                                             |
| Fraenkel et al 201050          | The United States | Adaptive conjoint analysis Recruitment from clinics | 140         | Hepatitis C               | Patients with higher severity of liver disease placed higher importance on benefits and less importance on risk of toxicity from therapy                                                                            |
| Fraenkel et al 200751          | The United States | Adaptive conjoint analysis Recruitment from centers | 185         | Osteoporosis              | Preference for injectable treatments was stronger among women with a relatively higher perceived risk of fracture                                                                                              |
| Fu et al 201652                | The United States | Standard gamble Recruitment from a cancer center | 107         | Metastatic colorectal cancer | Patients at stage IV had greater willingness to tolerate treatment related adverse events than those at stage III                                                                                               |
| Gallagher et al 200553         | The United States | Questionnaire Recruitment via a patient panel | 2444        | Migraine                  | Patients reporting more severe headaches preferred treatment with higher speed of onset whereas patients with milder headaches preferred treatment with no side effects                                           |

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| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|--------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Gray et al 2009<sup>54</sup>  | Canada    | Rating survey Recruitment via a patient panel | 100         | Ulcerative colitis   | Patients experiencing disease flare put more importance on speed of symptom relief and less importance on side effects |
| Hauber et al 2017<sup>55</sup> | The United States | Discrete choice experiment Recruitment via a patient panel and a patient association | 599         | Chronic hand eczema  | Patients with limitations on daily activities due to severe eczema had higher maximum acceptable risk of adverse events estimates |
| Hauber et al 2009<sup>56</sup> | The United Kingdom and The United States | Discrete choice experiment Recruitment via an online panel | 407         | Type II diabetes mellitus | Patients with glycated haemoglobin above 7.5% placed more importance on benefits, including heart-attack risk and glucose control |
| Hilgsmann et al 2017<sup>57</sup> | Belgium, France, Ireland, the Netherlands, Spain, Switzerland and the United Kingdom | Discrete choice experiment Recruitment by mail | 1124        | Osteoporosis         | Patients with previous fractures put more importance on drug effectiveness, and are willing to pay more for medication than those without previous fractures |
| Hodgkins et al 2012<sup>58</sup> | The United States, The United Kingdom, Canada, and Germany | Discrete choice experiment Recruitment by local independent patient recruitment services | 400         | Ulcerative colitis   | Patients who experienced more recent flares had a greater preference for treatments that reduced flare risk |
| Howell et al 2017<sup>59</sup>  | Australia | Best-worst scaling Recruitment from transplant units and via an online patient panel | 93          | Immunosuppression after kidney transplantation | Having had more than 1 transplant and increasing comorbidities were both associated with greater concern for long graft survival |
| Johnson et al 2010<sup>60</sup> | The United States | Discrete stated choice survey Recruitment via an online panel | 576         | Irritable bowel syndrome | Patients with more severe symptoms had higher maximum acceptable risk for side effects than patients who had less severe symptoms |
| Kleiggaard et al 2014<sup>61</sup> | Denmark | Discrete choice experiment Recruitment from a public center | 348         | Low back pain        | Patients with higher score on the pain scale were less risk-averse than those with lower pain scores |
| Lacy et al 2015<sup>62</sup>  | The United States | Standard gamble Recruitment via mail using a data reporting system | 114         | Functional dyspepsia  | Patients with severe and/or mixed symptoms were willing to take more risks with a hypothetical medication |
| Lim et al 2019<sup>63</sup>    | The United States | Survey Recruitment from a patient registry and clinics | 676         | Systemic lupus erythematosus | Patients with disease damage had less concern of complications from treatment than those with no disease damage |
Table 3 (Continued).

| Reference, Year of Publication | Countries       | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results                                                                 |
|--------------------------------|-----------------|-----------------------------------------------|-------------|---------------------|---------------------------------------------------------------------------------|
| Manjunath et al 2012<sup>39</sup> | The United States | Discrete choice experiment/conjoint analysis Recruitment from a patient panel | 193         | Epilepsy            | Patients with no seizures in 3 last months were less likely to accept an add-on antiepileptic agent |
| Mantovani et al 2005<sup>64</sup> | Italy           | Discrete choice experiment Recruitment from centers | 178         | Hemophilia           | Patients with severe haemophilia had less concern about viral safety than those with moderate haemophilia |
| Meads et al 2017<sup>74</sup>    | The United Kingdom | Discrete choice experiment, willingness-to-pay Recruitment from care centers | 221         | Pain management in cancer | Patients with poor pain relief were less willing to wait for treatment |
| Nolla et al 2016<sup>63</sup>    | Spain           | Conjoint analysis Recruitment from hospitals | 488         | Rheumatic diseases   | Patients with more severe disease symptoms put higher importance on pain relief and improvement in functional capacity |
| O’Brien et al 1990<sup>69</sup>  | The United Kingdom | Questionnaire/ Standard gamble Recruitment from a specialized hospital | 100         | Rheumatic diseases   | Patients’ willingness to accept risk increases with reductions in self-assessed health status |
| Ratcliffe et al 2004<sup>66</sup> | The United Kingdom | Conjoint analysis Recruitment by phone calls via a market research database | 412         | Osteoarthritis       | Patients with more severe symptoms put higher importance on pain reduction and lower importance on risk of serious side-effects than those with mild symptoms |
| Schaarschmidt et al 2018<sup>41</sup> | Germany         | Discrete choice experiment Recruitment in dermatology centers and via a patient organization | 222         | Psoriasis            | With increasing disease severity, patients had less concern regarding serious side effects |

Patients accepting less risk or cost with higher disease severity

| Reference, Year of Publication | Countries       | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results                                                                 |
|--------------------------------|-----------------|-----------------------------------------------|-------------|---------------------|---------------------------------------------------------------------------------|
| Hehir et al 2020<sup>104</sup> | The United States | Survey Recruitment via a patient society | 283         | Myasthenia gravis   | Patients treated with medications that could indicate more severe disease manifestation had more concern regarding potential adverse events |
| Johnson et al 2007<sup>24</sup> | The United States | Conjoint analysis Recruitment by an online panel and from clinical practice sites | 580         | Crohn’s disease     | Patients with more severe symptoms were less tolerant of serious adverse events risks than those with less severe symptoms |

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Table 3 (Continued).

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|--------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Kaehler et al 2016\textsuperscript{122} | Germany | Standard gamble/ Threshold questions Recruitment from skin cancer centers | 130 | Melanoma | Patients with pre-existing cancer had considerably higher threshold benefits for the chance of being melanoma-free at 5 years than those without any antecedent malignancy |
| Kuchuk et al 2013\textsuperscript{123} | Canada | Standard gamble Recruitment from cancer centers | 69 | Breast cancer | Patients with advanced disease placed less importance on survival benefit and higher importance on quality of life |
| Lee et al 2016\textsuperscript{124} | Korea | Discrete choice experiment/ trade-off/ Willingness-to-pay Recruitment in a cancer center | 102 | Advanced ovarian cancer | Patients without experience of recurrence were more likely to choose additional treatment and higher cost than those with experience of recurrence |
| Lewis et al 2020\textsuperscript{124} | The United Kingdom, The United States, and Germany | Discrete choice experiment Recruitment via recruitment agencies, patients support groups, and patient key opinion leaders | 450 | Chronic obstructive pulmonary disease | Patients who had experienced more exacerbations in the past put less importance on treatment efficacy in decreasing exacerbations in the next year |
| Lloyd et al 2005\textsuperscript{125} | The United Kingdom | Discrete choice experiment/ Willingness-to-pay Recruitment via a patient society | 148 | Epilepsy | Patients with higher seizure frequency had a lower willingness-to-pay for seizure control than those with lower seizure frequency |
| Marchesini et al 2019\textsuperscript{92} | Italy | Discrete choice experiment Recruitment from outpatient centers | 662 | Type 2 diabetes mellitus | Patients with higher body mass index put more importance on avoidance of risk of weight gain |
| Merlino et al 2001\textsuperscript{126} | The United States | Rating scale/ Time trade-off Recruitment from a university clinic | 107 | Rheumatoid arthritis | Patients who experienced a prior fracture had a higher preference to avoid potential fracture as a potential glucocorticoid-associated adverse event |
| Osilla et al 2011\textsuperscript{127} | The United States | Questionnaire Recruitment from HIV clinics | 127 | Hepatitis C and HIV coinfection | Patients with lower CD4 counts had a lower acceptance for additional hepatitis C treatment |
| Poulos et al 2016\textsuperscript{128} | The United States | Discrete choice experiment Recruitment by an online patient panel | 192 | Multiple sclerosis | Patients with mild symptoms placed greater weight on decreasing the number of relapses than those with moderate or worse symptoms |

(Continued)
Table 3 (Continued).

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Tada et al 2019\(^27\)       | Japan     | Discrete choice experiment Recruitment via a patient panel | 395         | Psoriasis            | Patients with lower disease severity gave more importance on sustained efficacy |
| Utz et al 2014\(^29\)        | Germany   | Conjoint analysis Recruitment from a hospital department | 156         | Relapsing remitting multiple sclerosis | Patients with higher disability scores were more likely to prefer pills over injections |

**No variation of patient preferences with disease severity**

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Bottomley et al 2017\(^18\)  | The United Kingdom | Discrete choice experiment Recruitment by a medical recruitment agency | 350         | Multiple sclerosis    | No significant differences in preferences found in sub-group analyses based on disease severity |
| Bröckelmann et al 2019\(^67\) | France, Germany, and The United Kingdom | Discrete choice experiment Recruitment from a research database | 381         | Hodgkin lymphoma     | Patient preference for progression free survival over overall survival was observed regardless of the stage of disease, early or intermediate/advanced |
| Choi et al 2009\(^20\)       | The United States | Interview Recruitment from a clinic | 52          | Asthma               | No differences found in patients’ perception of benefits or drawbacks of medicines according to disease severity |
| Gajra et al 2016\(^68\)      | The United States | Trade-off approach Recruitment of a subset of patients included in a randomised trial | 145         | Breast cancer        | Preferences for chemotherapy were not associated with hormone receptor status, performance status, or tumour and nodal stage |
| Havrilesky et al 2014\(^49\) | The United States | Discrete choice experiment/ Ranking and rating approaches Recruitment from a clinic | 95          | Ovarian cancer       | Similar preferences between patients with disease recurrence and those without |
| Hendriks et al 2018\(^50\)   | Columbia   | Best-worst scaling Recruitment from clinics | 195         | Human immune deficiency virus | No difference in preferences for treatment characteristics between patients with symptoms and those with no symptoms |
| Jarmolowicz et al 2017\(^71\) | The United States | Decision-making questionnaire Recruitment from a specialty clinic | 42          | Relapsing remitting multiple sclerosis | Patients with higher disability score did not have different decisions when weighing benefits and side effects of their medicines |
| Johnson et al 2009\(^23\)    | The United States | Discrete stated choice survey Recruitment from multiple patient panels | 651         | Multiple sclerosis    | Maximum acceptable risk for serious adverse effects did not change with, disability score, the number of relapses per year, or current multiple sclerosis category |

(Continued)
**Table 3** (Continued).

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Wong et al 2013²⁹             | The United States | Discrete choice experiment Recruitment from a cancer center and a community hospital | 400         | Cancer               | No association found between presence of metastases with patient preferences |

**Treatment Experience**

Fifty-eight studies (55% of total included studies) examined the dynamics of the evolution of patient-based BRA of medicines with previous treatment experiences (**Table 4**): 37 studies (64% of subset) reported an increased patient acceptance of risks, cost, or inconvenience with treatment experience, 10 studies (17% of subset) reported a decreased...

**Table 4** Studies Assessing the Variations of Patient-Based BRA of Medicines with Treatment Experience

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Patients accepting higher risk or cost with treatment experience | | | | | |
| Arroyo et al 2017³¹           | Spain     | Conjoint analysis Recruitment by treating neurologists | 221         | Relapsing remitting multiple sclerosis | Patients having previously received more than one disease-modifying therapy gave a higher importance to relapse rate reduction than patients receiving their first therapy |
| Bauer et al 2020³²            | Australia, Canada, Germany, Switzerland, and The United States | Discrete choice exercise Recruitment through local patient groups | 485         | Relapsing remitting multiple sclerosis | For those currently on injectable therapy, the administration route and dosing frequency were significantly less important compared with patients on oral therapy |
| Berry et al 2004³²            | The United Kingdom | Questionnaire Recruitment from a clinic | 81          | Rheumatoid arthritis and other painful musculoskeletal conditions | Treated patients had a greater perception of the effectiveness of treatment than those newly diagnosed |
| Beusterien et al 2007³³       | The United States and Germany | Conjoint survey Recruitment through advertisements in newspapers, in clinics, and via non-profit patient support centers | 288         | Human immunodeficiency virus | Treatment-experienced patients perceived the risk of severe rash to be less important than treatment-naive patients |

(Continued)
| Reference, Year of Publication | Countries                                                                 | Study Design and Recruitment of Participants                                                                 | Sample Size | Disease or Condition | Summary Results                                                                                                                                 |
|-------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Blinman et al 2016            | Australia and New Zealand                                                 | Time trade-off questionnaire Recruitment from sites participating in a study                                  | 83          | Endometrial cancer   | Patients who had adjuvant chemotherapy judged smaller benefits sufficient to accept therapy                                                                                     |
| Bruce et al 2018              | The United States                                                         | Questionnaire Recruitment from a clinic, via letters, and via advertisements online and in a specialized patient newsletter | 290         | Multiple sclerosis   | Patients who had never taken a disease-modifying therapy reported less willingness to take one                                                                  |
| Casciano et al 2011           | Algeria, Egypt, Iran, Lebanon, Morocco, Tunisia, Saudi Arabia, the United Arab Emirates, China, Malaysia, Thailand, Turkey, Argentina, Chile, Colombia, Guatemala, Mexico and Venezuela | Discrete choice modelling Recruitment from an international registry                                        | 14,033      | Diabetes mellitus    | Insulin-treated patients placed less importance on mode of administration (oral vs injection) than insulin-naive patients                                                                 |
| Cefalu et al 2008             | The United States, The United Kingdom, France, Germany, Spain, Mexico, and Brazil | Survey Recruitment from an international online patient database and via physicians                           | 1444        | Type 2 diabetes mellitus | Insulin-naive respondents were more averse to taking subcutaneous insulin in the future                                                                                                                                   |
| Desplats et al 2017           | France                                                                    | Questionnaire Recruitment from rheumatology departments of tertiary care hospitals                          | 201         | Rheumatoid arthritis | Patients who had another ongoing subcutaneous treatment preferred to switch from intravenous to subcutaneous, whereas patients only receiving intravenous treatment preferred not to switch |
| Dowson et al 2007             | The United Kingdom                                                        | Patient preference questionnaire Recruitment from a clinic                                                | 48          | Migraine             | With treatment experience, patients preferred the newer formulations more than conventional oral tablets                                                                                                                              |
| Duarte et al 2007             | France, Germany, Mexico, Spain, and The United Kingdom                    | Cross-sectional survey Recruitment through participating physicians and door-to-door by a designated interviewer | 3000        | Osteoporosis         | Higher percentages of untreated participants than treated participants ranked side effects and out-of-pocket expenses as the most important attributes |

(Continued)
| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Eliasson et al 2017<sup>30</sup> | The United Kingdom | Discrete choice experiment Recruitment via an online patient panel | 292 | Psoriasis | Participants with no prior exposure to biologic therapies were more averse to the risks of treatment toxicities compared with people with biologic exposure and biologic-experienced cohort was more willing to accept injection treatments |
| Emkey et al 2005<sup>31</sup> | The United States | Preference questionnaire Recruitment from centers | 342 | Osteoporosis | Treatment-naïve patients put more importance on convenience of treatment than experienced patients |
| Engelhard et al 2016<sup>32</sup> | Netherlands | Survey Recruitment via a patient monitoring society | 958 | Human immunodeficiency virus | With more treatment experience, patients put less importance on convenience of treatment |
| Fayad et al 2018<sup>48</sup> | Lebanon | Survey Recruitment by treating physicians in clinics and hospitals | 693 | Rheumatoid arthritis | Patients who experienced side effects from previous treatments had a higher preference for oral administration over subcutaneous or intravenous |
| Flood et al 2017<sup>33</sup> | The United States | Adaptive conjoint analysis survey Recruitment via a market research panel | 167 | Diabetes mellitus | Insulin-experienced and injection-experienced subgroups put less importance on regimen and mode of administration |
| Garcia-Dominguez et al 2016<sup>53</sup> | Spain | Discrete choice experiment Recruitment by patient associations | 125 | Multiple sclerosis | Treatment-naïve patients are more risk averse, put less importance on efficacy and more importance on route and frequency of administration |
| Grisanti et al 2019<sup>54</sup> | The United States and Canada | Survey Recruitment from clinical practices included in a larger study | 1841 | Rheumatologic diseases | Higher percentage of biologic-naïve patients overall expressed preference for intravenous therapy than for subcutaneous therapy than biologic-experienced patients |
| Ho et al 2020<sup>55</sup> | Australia | Discrete choice experiment Recruitment via consumer groups and an online consumer panel | 206 | Inflammatory arthritis | Biologic-experienced patients were more likely to accept injection and infusion treatments than biologic-naïve patients |

(Continued)
| Reference, Year of Publication | Countries            | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results                                                                                                                                 |
|-------------------------------|----------------------|-----------------------------------------------|-------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Huynh et al 2014              | Denmark              | Survey, Recruitment from university clinics   | 142         | Rheumatoid arthritis | Biologic-naive and biologic-experienced patients using subcutaneous injections preferred subcutaneous injections over infusion, whereas biologic-experienced on infusion still preferred intravenous administration at the clinic over self-injections |
| Johansson et al 2004          | Sweden               | Conjoint analysis questionnaire, Recruitment from centers | 298         | Asthma               | Patients on different treatments expressed variant preferences for attributes of alternative treatment                                      |
| Kowacs et al 2009             | Brazil               | Rating questionnaire, Recruitment from clinics | 203         | Migraine             | Patients overusing antimigraine medicines accepted having greater degrees of possible adverse events than those patients who did not overuse antimigraine drugs |
| Kromer et al 2015             | Germany              | Conjoint analysis, Recruitment from clinic    | 200         | Psoriasis            | Patients with more experience with systemic agents favoured sustainability of benefits                                                      |
| Lim et al 2013                | Singapore            | Questionnaire, Recruitment from a clinic      | 421         | Hepatitis B          | Treatment-experienced patients were willing to pay more for a higher efficacy than treatment-naive patients                                      |
| Lloyd et al 2011              | The United Kingdom   | Discrete choice experiment/ Willingness-to-pay Recruitment in clinics and via advertisement in newspapers | 485         | Diabetes mellitus    | Patients with previous experiences of hypoglycaemia as a side effect had a higher tolerance for this potential side effect and less willingness-to-pay to avoid it |
| Mansfield et al 2017          | Germany and Spain    | Discrete choice experiment, Recruitment from local communities and an online consumer panel | 875         | Type 2 diabetes mellitus | Patients with experience in injectable treatments put more importance on the efficacy of the medicine and less importance on the mode or frequency of administration |
| Marchesini et al 2019         | Italy                | Discrete choice experiment, Recruitment from outpatient centers | 662         | Type 2 diabetes mellitus | Previous experience with self-injectables strengthens patients’ willingness to accept injectable drugs                                       |
| Reference, Year of Publication | Countries          | Study Design and Recruitment of Participants                                                                 | Sample Size | Disease or Condition                  | Summary Results                                                                                                                                 |
|-------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------|-------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| McTaggart-Cowan et al 2008    | Canada             | Discrete choice experiment/ Willingness-to-pay Recruitment by a poster advertisement in a research clinic | 157         | Asthma                               | Patients using higher amounts of short-acting β-agonists had a greater preference for a treatment that resulted in more monthly symptom-free days |
| Morillas et al 2015           | Spain and Portugal | Discrete choice experiment, willingness-to-pay Recruitment from hospitals and clinics                       | 330         | Type 2 diabetes mellitus             | Patients receiving injectable treatment placed less importance on convenience attributes                                                    |
| Peyrot et al 2011             | The United States  | Survey Recruitment by an online patient panel                                                              | 1094        | Type 2 diabetes mellitus             | Patients taking only oral treatment had a higher interest in using inhaled insulin if available and avoiding injectables                   |
| Schaarschmidt et al 2011      | Germany            | Conjoint analysis Recruitment from a university medical center                                             | 163         | Psoriasis                           | Patients on injectables attach great importance to efficiency                                                                                        |
| van Heuckelum et al 2019      | The Netherlands    | Discrete choice experiment Recruitment from rheumatology departments                                       | 325         | Rheumatoid arthritis                 | Patients on injectable biologics put less importance on oral administration                                                                      |
| Verhoef et al 2018            | The Netherlands    | Maximum difference scaling/Interview Recruitment in a hospital rheumatology department and via electronic patient records | 214         | Rheumatoid arthritis                 | Patients with previous experience in dose reduction were more reluctant to de-escalate their current treatment                              |
| Vigneau et al 2019            | France             | Discrete choice experiment Recruitment in clinics                                                          | 789         | Anemia in chronic kidney disease     | With increasing experience with injectable treatments, patients put less importance on convenience such as frequency of injections            |
| Weilandt et al 2020           | Germany            | Discrete choice experiment Recruitment from dermatology centers                                           | 150         | Advanced melanoma                   | Patients who had been treated with immune checkpoint inhibitors regarded overall response rate as more important than did others and had less concern regarding immune related adverse events |
Table 4 (Continued).

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|-----------------------------------------------|-------------|----------------------|------------------|
| Weiss et al 2006<sup>99</sup>  | The United States | Forced ranking/ Survey Recruitment from a pool of respondents to national surveys | 999 | Osteoporosis | Treated patients placed more importance on effectiveness whereas untreated patients had a higher concern regarding side effects |
| Wong et al 2020<sup>100</sup> | Singapore | Discrete choice experiment Recruitment from a cancer center | 169 | Metastatic colorectal cancer | Patients naive to chemotherapy placed more importance on avoiding severe side effects |

Patients accepting lower risk or cost with treatment experience

| Blinman et al 2018<sup>101</sup> | Australia and New Zealand, and The United Kingdom | Validated preferences questionnaire Recruitment from trial sites | 233 | Renal cell carcinoma | Participants who experienced side-effects required larger benefits to warrant adjuvant therapy |
| Brotherston et al 2013<sup>102</sup> | Canada | Toxicity trade-off/ Semi-structured interviews Recruitment in a cancer clinic | 51 | Oropharyngeal cancer | Patients who underwent more than three cycles of chemotherapy were less willing to trade certainty of survival with avoiding toxicity than those treated with less cycles |
| Hardtstock et al 2020<sup>103</sup> | Germany | Discrete choice experiment Recruitment from multiple gastroenterology and hepatology centers | 108 | Chronic hepatitis B | Patients who experienced previous side-effects put more importance on safety profile than efficacy or route of administration |
| Hehir et al 2020<sup>104</sup> | The United States | Survey Recruitment via a patient society | 283 | Myasthenia gravis | Patients who experienced previous side-effects put more importance on safety profile than efficacy or route of administration |
| Islam et al 2019<sup>105</sup> | The United States | Ranking questionnaire Recruitment from cancer centers | 232 | Lung cancer | With more experience with chemotherapy, patients had tolerability for side effects decreased |
| Locadia et al 2006<sup>106</sup> | The Netherlands | Survey/ Interview Recruitment from clinics | 136 | HIV | Patients with more extensive experience with highly active antiretroviral therapy had a preference for a later initiation of therapy |

(Continued)
Table 4 (Continued).

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|--------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Mantovani et al 2005^54        | Italy     | Discrete choice experiment Recruitment from centers | 178         | Hemophilia           | The effect of viral safety was greater for patients taking recombinant treatment |
| Pacou et al 2015^130           | The United Kingdom | Discrete choice experiment Recruitment from a patient panel | 100         | Hepatitis C          | Patients currently receiving treatment put more importance on efficacy than those who already terminated their treatment course |
| Postmus et al 2018^107         | The United Kingdom | Multicriteria decision analysis Recruitment via a cancer charity | 560         | Multiple myeloma     | Patients who had previously experienced severe or life-threatening side effects attached a higher weight to mild or moderate chronic toxicity than to progression-free survival |
| Poulos et al 2019^108          | The United States | Discrete choice experiment Recruitment by a patient association and a patient panel | 250         | Endometriosis        | Patients who experienced moderate to severe hot flashes accepted less risk of increased hot flashes |

**No variation of patient preferences with treatment experience**

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|--------------------------------|-----------|---------------------------------------------|-------------|----------------------|-----------------|
| Chancellor et al 2012^131      | France, Germany, Italy, Spain, Sweden, and The United Kingdom | Discrete choice experiment/focus group Recruitment from international panels | 242         | Chronic pain         | No association found between variation in treatment history and preferences for attributes of opioids |
| daCosta DiBonaventura et al 2014^132 | The United States | Conjoint analysis Recruitment from cancer-specific online panels | 181         | Breast cancer        | Patient preferences did not vary with treatment experience |
| Das et al 2014^133             | The United Kingdom | Semi-structured interviews Recruitment by an early intervention team | 11          | Psychotic illnesses  | No association found between patients’ perceptions on antipsychotic long-acting injections and previous treatment |
| Fraenkel et al 2018^134        | The United States, Puerto Rico | Conjoint analysis Recruitment via a patient network, social media, respondent panel providers, and research companies | 1273        | Rheumatoid arthritis | No association found between current biologic use and patient preferences |

(Continued)
patient tolerance of risks, cost, or inconvenience with treatment history while 11 studies (19% of subset) found no association.

**Narrative Synthesis**

Our findings suggest that patient preferences may not have a clear association with disease duration. Half of the studies addressing the variation of patient-based BRA of medicines with disease duration (52%) reported no association between risk acceptance and disease duration,\(^{18-29}\) with fewer studies (35%) reported a higher tolerance for risk with more years

| Reference, Year of Publication | Countries | Study Design and Recruitment of Participants | Sample Size | Disease or Condition | Summary Results |
|-------------------------------|-----------|-----------------------------------------------|-------------|---------------------|-----------------|
| Fraenkel et al 2001\(^{21}\)  | The United States | Adaptive conjoint analysis Recruitment in community practices | 103         | Lupus nephritis     | No associations found between treatment history and patients’ preferences |
| Gelhorn et al 2019\(^{22}\)   | The United States | Discrete choice experiment/ Interview Recruitment from clinical sites | 47          | Severe asthma       | Treatment preferences were similar regardless of treatment status (corticosteroid or biologic) |
| Havrilesky et al 2014\(^{49}\) | The United States | Discrete choice experiment/ Ranking and rating approaches Recruitment from a clinic | 95          | Ovarian cancer      | Similar preferences found between patients currently receiving and those not receiving chemotherapy |
| Husni et al 2017\(^{135}\)    | The United States | Discrete choice experiment/ Willingness-to-pay/ Willingness-to-trade Recruitment from a clinic | 510         | Rheumatoid arthritis | Biologic-naïve patients had similar benefit-risk ratios and preferences for attributes to those who are biologic-experienced |
| Lewis et al 2020\(^{34}\)     | The United Kingdom, The United States, and Germany | Discrete choice experiment Recruitment via recruitment agencies, patients support groups, and patient key opinion leaders | 450         | Chronic obstructive pulmonary disease | Previous experience with side effects did not change the relative importance patients had put on attributes |
| Poulos et al 2016\(^{128}\)   | The United States | Discrete choice experiment Recruitment by an online patient panel | 192         | Multiple sclerosis  | No differences in preferences found between treatment naïve and treatment experienced patients |
| Turk et al 2020\(^{28}\)      | The United States | Discrete choice experiment/ Best-worst scenario Recruitment via patient panels | 602         | Osteoarthritis pain or chronic low back pain | No significant differences in patients’ preferences based on previous treatment experience |

**Abbreviations:** BRA, benefit-risk assessment; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology statement; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
since diagnosis whilst 13% reporting the opposite with more risk aversion with longer disease duration. There is a clearer association between patient preferences and disease severity with more than half of the studies (57%) identified in this category reported an increased risk tolerance with progressing disease severity whilst 17% of these studies found no association. There was a discernable association between patient treatment experience and increased risk tolerance (64%). Efficacy-related attributes as well as willingness-to-pay for more efficacious treatment gained more importance for patients with increasing experience with medicines. Safety-related attributes had more weight for treatment-naïve patients, but the importance diminished for patients with more treatment experience as they became more risk-tolerant. Process-related attributes, and particularly acceptance of injectable medications, changed considerably with treatment experience. Patients with more exposure to treatment were less concerned about the convenience of treatment and more open to using different formulations and routes of administration. Patients who had used injectable medicines placed less importance on mode of administration and convenience and were more willing to accept self-injectable treatments than patients who had not used these prior. However, not expectantly, previous experience of side effects was associated with patients becoming more risk averse. A model depicting the inter-relationship and dynamic impact of disease severity, disease duration and treatment experience on patients’ preferences and risk tolerance in chronic disease is represented in Figure 2.

**Discussion**

We identified 105 studies that investigated patient preferences of medicines’ attributes in a vast range of chronic conditions and explored preferences across three dimensions of disease duration, disease severity, and treatment experience. Most studies (81%) reported variations in patient preferences with one or more dimensions and only 19% found no association. The findings suggest that patient treatment experience, positive or negative, and disease severity are dominant factors that influence the dynamics of patient-based BRA of medicines. Disease duration seems to be a weaker contributor to these dynamics. In fact, time since diagnosis, when considered as an independent direct factor, provides increasing opportunities of preference reinforcement. However, in chronic disease, it is most often that with time patients...
may experience worsening of symptoms, more lines of treatments, and side effects.\textsuperscript{107} This may suggest that disease duration also provides circular reinforcement of the dominant factors influencing the dynamics of patient preferences.

Patients have an increasing risk tolerance and a greater willingness-to-pay with treatment experience during their disease journey.\textsuperscript{31–33,35,37,38,45,48,72–100} This may be explained by the impact of previous treatments on patients’ preferences.\textsuperscript{109} Although treatment-naïve patients are relatively more risk averse than treatment-experienced patients,\textsuperscript{79,99,100} the latter who had previously endured side effects become less risk tolerant.\textsuperscript{101,103,107,108} This is in line with the concept distinguishing patients’ perceptions ex-ante (prior to an event/anticipated) and ex-post (after the event/experienced),\textsuperscript{110} when a direct experience of a serious adverse event may alter how patients assess the BRA of their medicines. They may overemphasize risk and overestimate the severity of potential side effects.\textsuperscript{111} For example, patients with multiple myeloma who had previously experienced severe or life-threatening side effects put more importance on low toxicity than on progression-free survival.\textsuperscript{107}

Another salient result is the increased acceptance of injectable treatments, notably self-administration, among patients who had already used this mode of administration. For example, insulin-naïve patients are more averse to taking subcutaneous insulin in the future\textsuperscript{76} whereas insulin-treated patients placed less importance on mode of administration.\textsuperscript{75} Abu Hassan et al found that negative concerns about the use of insulin such as self-injection, needle phobia, inconvenience, and embarrassment are significantly higher in insulin-naïve diabetic patients than in experienced insulin-user diabetic patients.\textsuperscript{112} This is confirmed by the increased use of subcutaneous injectable devices, driven by increased users’ satisfaction with respect to convenience, ergonomics, and portability.\textsuperscript{113}

Moreover, we found that patients with higher disease severity,\textsuperscript{42,50,52} more pronounced symptoms,\textsuperscript{46} or increased disease damage\textsuperscript{49} placed higher importance on efficacy and less importance on the safety profile and cost. Indeed, patients may tolerate more severe potential side effects when their disease progression negatively affects their quality of life. For example, patients with inflammatory bowel disease develop a greater acceptance for potential risks of treatment when their condition worsens, in a desperate search for a cure.\textsuperscript{114} It remains inconclusive how disease duration, as an independent factor, alters patient preferences. The contrast across these dimensions suggests that factors important for patients’ assessment of benefits and risks of their medicines during a chronic disease journey will vary more with their clinical situation and previous treatment experience than with time since their diagnosis.

The studies revealed a range of strategies to elicit patient preferences. Conjoint analysis methods (especially discrete choice experiments) were the most frequently used, but there were 15 different methods employed in the studies reviewed. This mirrors the overall upward trend observed in the use of patient preferences elicitation methods over the last decade.\textsuperscript{115} There is currently no comprehensive comparison of these emerging methods, but increasing publications are providing guidance to select the most appropriate approach for a given application.\textsuperscript{116–118}

What are the implications for discussing benefits and risks of medicines with patients, at different points along their disease journey? Treatment paradigms and recommendations are shifting to earlier and more aggressive treatments. For example, in rheumatoid arthritis there is a “window of opportunity” in the first three months of disease onset to prevent damage occurring.\textsuperscript{119} Our results suggest that patients will be more risk averse and concerned during this phase, although they will become more risk tolerant and put higher importance on efficacy with more experience with treatment or when their symptoms become more severe. It is critical that patients and clinicians adequately understand that individual BRA may change.

Understanding the dynamics of patient-based BRA is also important when considering patient preferences in regulatory decisions. Having patients directly involved in the decision-making process or using evidence derived from patients in empirical studies should be routinely utilised as part of the evidence considered.\textsuperscript{4,120} Such input must be balanced and derived from cohorts of patients at different points of their disease journey and with different levels of exposure to treatments.

Despite the current evidence of the dynamics of patient-based BRA of medicines during the disease journey, only 105 out of 544 identified in the title and abstract screening had sub-group analyses based on disease duration, disease severity, or treatment experience. Due to the importance of these dimensions on patient preferences and potential impact on patients’ decision-making and clinical outcomes, there is a need for more studies to assess changes: larger studies that may be statistically powered for such sub-group analyses; the use of different methodologies; or longitudinal studies.
Strengths and Limitations

This is the first study, to our knowledge, to systematically review evidence of the dynamics of patient-based BRA of medicines in chronic diseases. The strengths of our review include the registered protocol, a validated search strategy, pre-specified eligibility criteria, and duplicate screening and data extraction.

This review has several limitations. Given the methodological and clinical heterogeneity of included studies, it was not possible to draw robust conclusions or conduct a meta-analysis. Therefore, we considered a narrative synthesis to be the most suitable format. We note that such a review is subject to a higher bias than a quantitative systematic review. However, the strong and consistent trends across the varied methods and wide range of chronic diseases studied support our proposed dynamic BRA model.

This review encompassed studies from various chronic conditions, with substantial differences in the burden of the disease on the patients as well as the efficacy-safety profile of suggested treatments. Moreover, studies included were not longitudinal. They assessed patients’ BRA of their medicines at one point of their disease journey when there may be other unidentified individual factors impacting patients’ perspectives.

Conclusion

This study identified and reviewed a large body of literature regarding the dynamics of patient-based BRA of medicines during the disease journey in chronic conditions. We conclude that factors impacting patients’ risk tolerance vary more with their disease severity and previous treatment experience than with time since diagnosis. These findings may be utilized to provide context for patient centered clinical decision-making around the use of medicines in chronic disease.

Key Points for Decision Makers

- Patient assessment of benefits and risks of medicines in chronic conditions is likely to evolve during the disease journey
- Patients with increased treatment experience tend to become more risk tolerant
- Patients with experience in self-injectables have a higher acceptance for this mode of administration
- Patients with increased disease severity are willing to accept higher risks to achieve improved clinical outcomes
- Patients with experiences of side effects may become more risk averse

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Author Contributions

All authors made a significant contribution to the review reported, whether that is in the conception, design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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