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Two approaches for diagnosis of nonsteroidal anti-inflammatory drug hypersensitivity in children

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ABSTRACT

Background: The oral provocation test (OPT) with culprit drug is the gold standard in the diagnosis of nonsteroidal anti-inflammatory drug hypersensitivity (NSAID-H). Some authors have proposed that the total number of OPTs required to diagnose NSAID-H is much lower with acetyl salicylic acid (ASA) provocations, regardless of patients' reaction history, and less time consuming.

Objective: This study aims to evaluate the total number of OPTs required to confirm NSAID-H according to the drugs (ASA or culprit NSAID) used in the initial OPT.

Methods: The study included patients with a history of NSAID-H. Data on the demographic and clinical features, coexisting chronic or allergic disease, and laboratory results were collected from medical records. The drug used for the initial OPT (ASA or culprit NSAID), results of the OPT, and the total number of OPTs were reviewed.

Results: We included 56 children with suspected hypersensitivity reaction to NSAIDs. NSAID-H was confirmed in 21 children (37.5%). We calculated that if all OPTs were performed with culprit drugs as an initial choice, the number of OPTs required for diagnosis would be 3 or more in 85.7% of positive cases. The number of episodes was an independent risk factor for NSAID-H by multiple logistic regression analysis (odds ratio, 4.3; 95% confidence interval, 1.48-12.24; $P = .007$).

Conclusion: Performing an initial OPT with ASA regardless of patients' reaction history can result in much lower numbers of OPT to diagnose NSAID-H and can improve patient compliance.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of fever and pain in children.[1] Nonsteroidal anti-inflammatory drug hypersensitivity (NSAID-H) is 1 of the most common causes of drug-induced hypersensitivity reactions in the pediatric population.[2]

According to the timing of the reaction, NSAID-H is divided into 2 types: acute reactions (immediate to several hours after exposure) and delayed reactions (more than 24 hours after exposure). Reactions to NSAIDs may be induced by a single drug (selective reactions [SR]) via an immunologic mechanism (immunoglobulin E [IgE]-mediated or T cell–mediated), which is called an allergic reaction, or may be induced by multiple NSAIDs via the cyclooxygenase enzyme inhibition, which is responsible for cross-reactivity between NSAIDs with different chemical structures and is called a non-allergic reaction (cross-intolerant [CI]).[3,4] The European Network for Drug Allergy (ENDA) classification has identified 2 groups of SRs and 3 groups of CIs (Table 1). These phenotypes are mainly based on authors' expertise and studies that were conducted on adult populations.[5-7]Although several studies have been published, the classification according to the clinical phenotypes in children is still inadequate.[8-12]

Although skin prick/intradermal (ID) tests might be helpful for research purposes in IgE-mediated reactions, the oral drug provocation test (OPT) with the culprit NSAID is the gold standard in the diagnosis of NSAID-H.[13,14] According to the recommendations that reporting in previous studies, the OPT with aspirin to those who report a reaction to multiple NSAIDs is a possible approach to diagnosis. Another approach for provocation is performing an initial OPT with aspirin regardless of the patient's reaction history and an additional OPT with the culprit drug in the case of a negative OPT with ASA.[15,16] Blanca-Lopez et al[16] reported that the total number of OPTs required to diagnose NSAID-H was much lower with initial ASA provocations; the authors suggest that initial ASA provocation is less time consuming, and when a reaction occurred

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Table 1
The Characteristics of Patients Who Were Diagnosed With NSAID-H

Patient	Age	Atopy/allergic disease	Culprit drugs	Initial OPT (cumulative dose, %)	Reaction during OPT	Safe alternatives	Class
1	5.2	-/-	Ibuprofen Metamizol	Aspirin (23)	Urticaria-angioedema	Acetaminophen	CI
2	5.3	HDM/-	Ibuprofen	Aspirin (30)	Urticaria-angioedema	Acetaminophen	CI
3	3.8	-/-	Ibuprofen	Ibuprofen (100)	Urticaria	Not performed	SR
4	7.5	-/Drug allergy	Ibuprofen Metamizole	Ibuprofen (100) Metamizole(60)	Urticaria Urticaria-angioedema	Acetaminophen, Acetaminophen	CI
5	13	HDM/asthma	Ibuprofen	Ibuprofen(100)	Anaphylaxis	Acetaminophen	CI
6	14	HDM/Rhinitis	Diclofenac Metamizole Acetaminophen	Aspirin (25)	Anaphylaxis	Acetaminophen	CI
7	2	-/CU	Ibuprofen Acetaminophen	Ibuprofen (100) Acetaminophen	Urticaria Not reaction	Acetaminophen	SR
8	3.8	-/-	Ibuprofen	Aspirin (10)	Urticaria	Acetaminophen	CI
9	5.3	Alternaria/Asthma	Ibuprofen	Aspirin (10)	Asthma	Acetaminophen	CI
10	18	Pollen/Asthma	Ibuprofen	Aspirin (10)	Angioedema	Acetaminophen	CI
11	15.2	HDM/Asthma	Ibuprofen	Aspirin (100)	Urticaria	Acetaminophen	CI
12	15	Pollen/Asthma	Ibuprofen	Aspirin(25)	Asthma	Acetaminophen (Nimesulide not tolerated)	CI
13	6.5	-/CU	Ibuprofen	Aspirin (10)	Urticaria	Acetaminophen	CI
14	16.3	-/-	Unknown	Aspirin (10)	Urticaria	Acetaminophen	CI
15	15	-/-	Flurbiprofen	Aspirin	Tolerated (Urticaria with Flurbiprofen)	Acetaminophen	SR
16	3.3	-/-	Ibuprofen Aspirin	Aspirin (33)	Urticaria	Acetaminophen	CI
17	17	HDM/Asthma	Flurbiprofen	Aspirin (15)	Angioedema	Acetaminophen Nimesulide	CI
18	7	-/-	Ibuprofen	Ibuprofen (100)	Urticaria	Acetaminophen	CI
19	15.7	-/-	Ibuprofen Flurbiprofen	Ibuprofen(30) Flurbiprofen (100)	Urticaria Urticaria	Acetaminophen	CI
20	12	HDM, pollen/ rhinitis	Ibuprofen Acetaminophen	Aspirin (30)	Angioedema	Acetaminophen Nimesulid	CI
21	10	HDM/asthma	Ibuprofen	Aspirin(10)	Urticaria	Acetaminophen	CI

CI, cross-intolerant; CU, chronic urticaria; HDM,; IgE, immunoglobulin E; NSAID-H, nonsteroidal anti-inflammatory drug hypersensitivity; OPT, oral provocation test; SD, standard deviation; SR, selective reactions.

with the culprit NSAID that was used for the initial OPT, patients left the study, which is the reason for the noncompleted studies.[8]

This retrospective analysis aims to identify (1) the frequency of confirmed NSAID-H in children with a history of a reaction with NSAIDs; (2) the total number of OPTs required to confirm NSAID-H according to the drug (acetylsalicylic acid [ASA] or culprit NSAID) used in the initial OPT; (3) possible risk factors for an NSAID-related hypersensitivity reaction; and (4) safe alternative drugs for children with proven NSAID-H.

Methods

This retrospective study was conducted in the Department of Pediatric Allergy and Immunology at Kocaeli University, Turkey. All children who underwent an OPT with NSAIDs in our outpatient clinic between January 2014 and December 2017 were included in the study. Written informed consent was obtained from the parents, and the local ethics committee approved the study at Kocaeli University.

The OPTs were performed using 2 different approaches based on the drug used in the initial OPT at different times in our department. One approach was an initial OPT with ASA. In the case of a positive result with the ASA provocation, patients were defined as cross-intolerant (CI), and additional OPTs were performed to find a safe alternative at least 4 to 6 weeks after the previous OPT. In the case of a negative result, an OPT with the culprit NSAID was performed. Patients who had a positive OPT result with culprit NSAIDs were defined as selective responders (SR). The second approach was an initial OPT with the culprit NSAID. An ASA provocation was performed to assess for CI if the initial OPT result with the culprit NSAID was positive.

In all children with proven NSAID-H, an additional OPT with acetaminophen (also known as paracetamol) was performed to find a safe alternative; nimesulide was used in children older than 12 years. Antihistamines and all medications that might influence the outcome of the provocation tests were stopped at least 1 week before the test. Four or 5 increasing doses of NSAIDs, starting from low doses (1/10 of therapeutic doses) were given orally at intervals of 60 minutes up to a single cumulative dose. The doses were administered according to the recommendations of ENDA.[15] A maximum of 5 doses were administered to prevent the possibility of desensitization. If no symptoms appeared during the OPT, the cumulative therapeutic dose appropriate for the patient's age and weight was reached. The outcome of the challenge was recorded as positive at any time during the challenge when symptoms appeared and the OPT was stopped and the reaction treated accordingly. Patients were monitored in the clinic for at least 2 hours after the last dose. If no symptoms appeared, the OPT was recorded as negative. Patients were asked to contact the clinic if there was a delayed reaction.

Data on the demographic and clinical features, coexisting chronic or allergic disease (such as chronic spontaneous urticaria, asthma, nasal polyps, chronic rhinosinusitis, allergic rhinitis), test results (complete blood cell count, total IgE, skin prick tests for aeroallergens), and standardized ENDA drug allergy questionnaires on drug allergy were collected from the medical records. The drug used for the initial OPT (ASA or culprit NSAID), results of the OPTs, the total number of OPTs (to diagnose and to find a safe alternative

drug) were reviewed. Considering the OPT results, the estimated total number of OPTs for 3 approaches were calculated for patients with confirmed NSAID-H

1. if an initial OPT with ASA was performed
2. if an initial OPT with culprit NSAID was performed
3. if an initial OPT with ASA in the case of suspected reaction to multiple NSAIDs and with culprit drug in those who had a suspected reaction to a single NSAID was performed

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as means ±standard deviation, medians (25^{th}-75^{th} percentiles); and categorical variables were expressed as counts (percentages). Comparisons of normally distributed continuous variables between the materials/groups were performed by using the Student's *t* test. Comparisons of non-normally distributed continuous variables between the groups were performed by using the Mann-Whitney *U* test. Comparisons of abnormally distributed continuous variables between the times were performed by using the Wilcoxon *t* test, Friedman analysis of variance by ranks, and Tukey post hoc test. Comparisons of categorical variables between the groups were performed using the Fisher's exact χ^2 test, Yates χ^2 test, and Monte Carlo χ^2 test. A multiple logistic regression analysis was conducted to determine independent risk factors for NSAID-H by including all variables that identified with the univariate analysis.

Results

The study included 56 patients (28 females, 28 males) with suspected NSAID-H. Median age at the time of the OPT was 7.12 years (range, 1.25-18 years). The mean time interval (±SD) between the last reported reaction to the drug and the OPT was (11.89 ± 16.07) months (range, 1.5-72 months), and median interquartile range was 4.6 months. The interval between the drug intake and the occurrence of symptoms in clinic history was less than 1 hour in 66.1% of the children. None of the patients had a delayed reaction (more than 24 hours after exposure). Thirty-five patients (62.5%) described a reaction to a single NSAID. According to the allergic reaction to other drug classes, parents reported a previous reaction in 13 (23.2%) of the children, but only 1 child had confirmed allergy against beta-lactam antibiotics (we performed an allergy workup for each patient in our center). Ibuprofen was the most commonly reported drug (76.8%), followed by acetaminophen (32%). The most common clinical manifestation was urticaria (53.5%). Otherreported reactions were isolated angioedema (26.8%), urticaria-angioedema (12.5%), anaphylaxis (3.6%), respiratory manifestations with angioedema (1.8%), and isolated respiratory manifestations (1.8%). Fourteen children (25%) revealed atopy via skin prick testing, and 6 patients (10.7%) had a parental history of NSAID-H.

Comparison of Initial OPTs with ASA and Culprit NSAID According to the Total Number of OPTs Required for Diagnosis and Safe Alternatives

We aimed to estimate the total number of OPTs for ASA and other drugs used in the initial OPT in patients with confirmed NSAID-H. We also calculated the total number of OPTs if an initial OPT was performed according to an algorithm (initial OPT with ASA in case of suspected reaction to multiple NSAIDs and with culprit drug in those who reaction to a single NSAID). When we compared the 3 approaches, we found a significant difference. In the case of an initial OPT with culprit NSAID, 85.7% of cases with NSAID-H would have required 3 or more OPTs. In the case of an initial OPT with ASA, 3 or more OPTs would have been required in 14.3% of patients with NSAID-H, whereas with the algorithm the ratio would be 47.6% . The total number of OPTs for the 3 approaches is given in Table 2.

The Result of OPTs for Diagnostic Purposes and Safe Alternatives

We performed an initial OPT with culprit NSAID in 26 patients and with aspirin in 30 patients. Of the 56 patients, 21 (37.5%) were confirmed to have NSAID-H. Of the 7 patients who had a positive initial OPT against culprit NSAID, 2 patients tolerated ASA, and 5 patients had a positive OPT result with ASA. Thirteen patients had a positive initial OPT result with ASA, and 1 patient who had a negative initial OPT with ASA tolerated the culprit drug. Of the 21 cases with NSAID-H, 18 patients (85.7%) were therefore classified as CI and 3 as SR (Fig 1).

Twenty patients with NSAID-H were challenged to find a safe alternative (17 with acetaminophen, 3 with acetaminophen and nimesulide). One patient developed bronchospasm with nimesulide, and no reaction occurred when acetaminophen was given. None of the other patients developed reactions (Table 1).

Risk Factors Related to Confirmed NSAID-H

No significant differences were found regarding sex, history of clinical symptoms, the NSAID involved, previous reaction to another drug class, the time between last reported reaction to culprit drug and OPT, peripheral eosinophilia, and the presence of NSAID-H in the family between the patients with NSAID-H and tolerant patients. The children with NSAID-H were older at the time of the first OPT (10.04 ± 5.33 years) than the tolerant patients (7.22 ± 4.52 years). Immediate reactions (≤1 h) after drug intake were more frequently reported in patients with proven NSAİD-H compared with tolerant patients (86 vs 54%, $P = .03$). Comparison of the clinical and laboratory profiles of the children with proven NSAID-H and tolerant children is shown in Table 3. Of the 21 patients with NSAID-H, 10 (47.6%) had confirmed sensitization by skin prick testing; atopy in patients without NSAID-H was 11.4% ($P = .007$). Twenty-three (65.7%) tolerant patients reported only 1 previous reaction, whereas patients with NSAID-H had more than 1 previous reaction to an NSAİD with a statistically significant difference (76%, $P = .001$). If we consider the presence of a previous reaction to only unrelated NSAİDs, no significant difference was seen between the patients with proven NSAİD-H and tolerant patients (47.6 % vs 34%, $P = .32$).

In the multiple logistic regression analysis, the only independent factor that showed significance was the number of episodes (odds ratio, 4.3; 95% confidence interval, 1.48-12.24; $P = .007$).

Classification of Patients with NSAID-H According to the ENDA Classification

The patients with proven NSAID-H were further classified as NSAID-induced urticaria/angioedema (n = 12), NSAID-exacerbated

Table 2
The Estimated Number of OPT According to the Initial OPT

	Initial OPT with culprit NSAID	Initial OPT with ASA	Initial OPT with algorithm	*P*
Mean ± SD	3,28 ± 0.71	2,14 ± 0.35	2,57 ± 0.67	<.001
Total number of OPT, n (%)				
1	0	0	0	
2	3 (14.4%)	18 (85.7%)	11 (52.4%)	
3	9 (42.8%)	3 (14.3%)	8 (38.1%)	
4	9 (42.8%)	0	2 (9.5%)	

ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; OPT, oral provocation test.

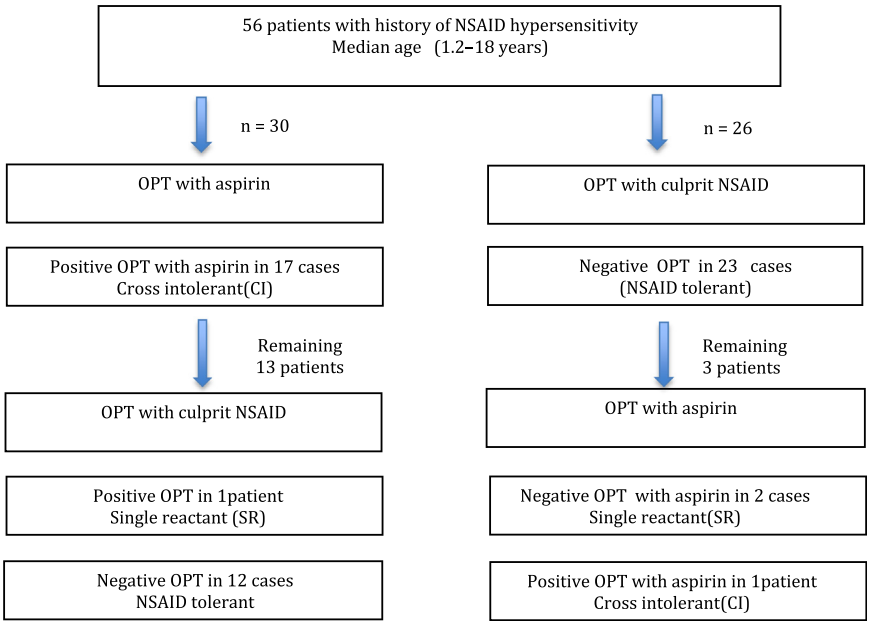

Figure 1. Diagnostic flow chart.

cutaneous disease (n = 1), NSAID-exacerbated respiratory disease (n = 2), and single NSAID-induced urticaria/angioedema or anaphylaxis (n = 3). Three cases of CI could not be categorized according to the ENDA classification system, because 2 of them had bronchospasm and facial angioedema, and 1 had respiratory symptoms without a previous history of asthma (Table 4).

Discussion

In the current study, NSAID-H was confirmed by OPT in 21 (37.5%) patients. These findings are similar to previous studies that included children.[10,16,17,19,20] Viola et al[21] found that 78.8% of patients with suspected NSAID-H tolerated the culprit drug in an OPT. İn our study, 62.5% of children with a history compatible with hypersensitivity reactions after NSAİD intake were confirmed as tolerant in OPT. In many children who develop urticaria during acute infectious episodes, these reactions are often falsely attributed to the drug used, which demonstrates the significance of performing oral drug provocation tests.

As a result, considering CI vs SR, most of our cases were CI, which is consistent with previous studies. The proportion of CI in children varies from 40% to 80%.[9,11,16,17] The determination of cross-reactivity based on history in children with NSAID-H may be misleading. In our study, 8 (50%) children with CI reacted to a single NSAID, and a patient who had suspected reactions to multiple NSAIDs was an SR. Children with CI could not be excluded in the study groups when only the culprit drug was given, which suggests the overestimation of SR. This situation demonstrates the significance of performing a provocation with ASA to determine CI.

Table 3
Characteristics of the Proven NSAID-H Patients and the NSAID-Tolerant Patients

	Proven NSAID-H (n = 21)	NSAID-tolerant (n = 35)	*P*
Age at OPT time (years) (mean ± SD)	10.04 ± 5.33	7.22 ± 4.52	.04
Sex (male)	12/21(57%)	16/35 (45.8%)	NS
Drug involved (%)			
Ibuprofen	17/21 (81%)	27/35 (75%)	
Acetaminophen	4/21	14/35	
Flurbiprofen	3/21	2/35	
Metamizole	4/21	0/35	
Naproxen	0/21	2/35	
Diclofenac	1/21	1/35	
Aspirin	1/21	1/35	
Reaction interval after drug intake, <1 hr	18/21 (86%)	19/35 (54%)	.03
Symptoms on admission			
Urticaria (with/without angioedema)	11/21 (52.4%)	26/35 (74.2%)	NS
Angioedema	7/21 (33.3%)	8/35 (22.8%)	NS
Anaphylaxis	2/21 (9.5%)	1/35 (2.8%)	NS
Respiratory manifestation	1/21 (4.7%)	0/35 (0%)	NS
The time between last reported reaction and OPT, months (mean ± SD)	14.27 ± 15.50	10.47 ± 16.34	NS
Atopic sensitization	10/21 (47.6%)	4/35 (11.4%)	.007
Family history of NSAID-H	3/21 (14.3%)	3/35 (8.6%)	NS
No. of episodes, mean ± SD)	2.14 ± 0.96	1.37 ± 0.54	.001
Serum total IgE (IU/mL), (mean ± SD)	210.2 ± 155.1	136.4 ± 238.4	.008
Serum eosinophilia, (mean ± SD)	203.3 ± 184.3	211.5 ± 186	NS

IgE, immunoglobulin E; NSAID-H, nonsteroidal anti-inflammatory drug hypersensitivity; OPT, oral provocation test; SD, standard deviation.

Table 4
Classification of NSAID Hypersensitivity According to the ENDA Classification

	n (%)
1. NSAID-exacerbated respiratory disease (NERD)	2 (9)
2. NSAID-exacerbated cutaneous disease (NECD)	1 (4,5)
3. NSAID-induced urticaria/angioedema (NIUA)	12 (59, 1)
4. Single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA)	3 (13, 6)
5. Single NSAID-induced delayed reactions (SNIDR)	0
Unclassified	3 (13, 6)

NSAID, nonsteroidal anti-inflammatory drug.

After a confirmed diagnosis of NSAID-H, additional OPTs for the classification of the reaction and safe alternatives, especially in children with cross-intolerant reactions, should be performed. In the case of an initial OPT with a suspected drug, at least 3 visits should be planned for these purposes in many patients. According to a study by Blanca-Lopez et al,[16] who included an initial OPT with ASA, the total number of OPTs required to diagnose was much lower compared with the other studies. These authors also reported that the risk for noncompletion of the study was the occurrence of a reaction in patients who were given the culprit drug in the initial OPT. The use of ASA in children is a concern because of the risk of Reye syndrome; therefore, a limited number of studies have been performed on the use of ASA for evaluation of CI or in the diagnosis of the NSAID-H. Acetylsalicylic acid may cause cellular mitochondrial damage, which results with the inhibition of fatty acid metabolism in the setting of viral disease. Epidemiologic studies found that <0.1% of children who took ASA developed Reye syndrome; in conditions such as lack of viral infection, Reye syndrome is less likely.

In contrast to other centers, we did not follow the same diagnostic algorithm in all patients for reactions of suspected NSAID-H. The OPTs were performed using 2 different approaches concerning the drug used in the initial OPT. One of the aims of this study was to retrospectively estimate the total number of OPTs for each drug (ASA and culprit NSAIDs) if they were used in an initial OPT. When we compared these approaches, there was a significant difference. In the case of an initial OPT with ASA, only 14.3% of patients with NSAID-H would have required 3 or more OPTs. We think that an initial OPT with ASA may be less time consuming and more comfortable, especially for patients who cannot attend additional visits and live in areas that are distant from clinics.

When SR and CI were further classified according to the ENDA/GA2LEN classification, 3 (14.3%) patients could not be categorized based on the underlying disease and clinical manifestations. Previous studies reported that some children with proven NSAID-H could not be classified according to the possible phenotypes described by the ENDA group.[3] This classification was based on the authors' expertise in adolescents and adults with hypersensitivity reactions to NSAIDs.

The response to acetaminophen in patients who are CI has been reported to be up to 25% in children.[17,22-24] In this study, we performed OPTs with acetaminophen as a safe alternative drug in all patients (except 1) with NSAID-H. None of the patients developed a reaction to high doses of acetaminophen, which is consistent with results of a previous study by Zambonino et al.[9] We performed OPTs with nimesulide in only 3 children because we had a limited number of patients older than 12 years, and some refused an OPT with this drug after they tolerated acetaminophen. One patient who tolerated acetaminophen reacted to nimesulide, and 2 other patients tolerated both drugs as safe alternatives.

In multivariate logistic regression analysis, only the number of episodes was identified as a significant independent risk for proven NSAID-H. Although a positive association with respiratory involvement, the number of drugs involved, a family history of NSAID-H, and sex have been reported in the literature, we did not find a significant association between these factors and NSAID-H.[17–19,25]

In conclusion, we show that the rate of CI reactions in children is much higher than that of SRs, and performing an initial OPT with ASA can improve patient compliance because of a much smaller number of OPTs.

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