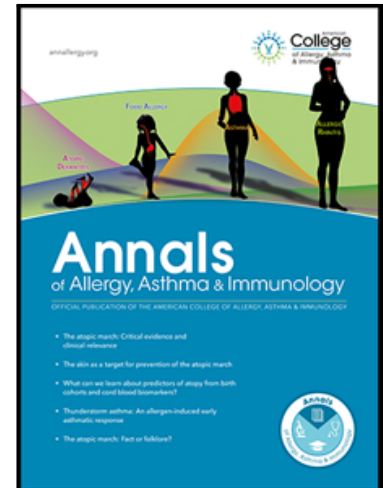


Recent Development on the use of SLIT tablets for Allergic Rhinitis

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1 TITLE:

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3

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21 **Conflicts of Interest Disclosures:**

22 Dr. Wasserman reports the following financial relationships: Aimmune Therapeutics, Medexas,
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27 Ms. Shah reports no conflicts.

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32 Objective Allergic rhinitis (AR) is an IgE-mediated inflammatory condition that causes symptoms of
33 sneezing, nasal congestion, rhinorrhea, and nasal itch. Although subcutaneous immunotherapy (SCIT)
34 for the treatment of AR has been in use and well established as a treatment modality, sublingual
35 immunotherapy (SLIT) is increasingly considered to be the safer and more convenient alternative. Thus,
36 the objective of this review is to describe recent findings pertaining to the use of SLIT tablets (SLIT-T) for
37 AR.

38

39 Study Selections A total of 11 RCTs were selected for full-text review and included in the analysis. All
40 studies investigated the use of SLIT on patients with seasonal allergic rhinitis (4 tree pollen studies, 1
41 grass pollen study, 1 Japanese Cedar) or perennial allergic rhinitis (3 house dust mite studies).

42

43 Data Sources:

44

A database search (PubMed.gov) for articles published between January 1 st , 2017 to February 9 th , 2021 was conducted using the following key words: “allergic rhinitis”, AND-ed “sublingual immunotherapy”. Included were randomized placebocontrolled trials (RCTs). Other experimental designs studies were excluded.

Results

Our review of 7 recently published randomized placebo-controlled trials with 2348 subjects receiving SLIT, reported increased efficacy, safety, supportive immunological parameters (IgE and IgG4 levels pre- and post-treatment levels) and improved quality of life. All studies excluded subjects with overlapping seasonal or perennial allergens, a history of moderate to severe, uncontrolled asthma or reduced lung function.

Conclusion:

Our review highlights that SLIT is a safe and effective treatment that significantly reduces symptoms and medication requirements in allergic rhinitis, and improved quality of life.

Keywords:

Allergic rhinoconjunctivitis, rhinitis

allergy immunotherapy

birch pollen

grass pollen

house dust mite

clinical efficacy

70 clinical trial

71 safety

72 sublingual immunotherapy tablet

73 total combined score

74 tree pollen

75

76 **Abbreviations:**

77 AE Adverse event

78 ARC Allergic rhinoconjunctivitis

79 AR Allergic rhinitis

80 BPS Birch pollen season

81 RQLQ Rhinoconjunctivitis Quality of Life Questionnaire

82 SLIT Sublingual immunotherapy

83 SCIT Subcutaneous immunotherapy

84 SQ Standardized quality

85 TNSS Total nasal symptom score

86 TPS Tree pollen season

87 BPM Birch pollen season

88

89

90 INTRODUCTION

91 Allergic rhinitis (AR), which can occur with or without conjunctivitis (C), is an IgE-mediated inflammatory
92 condition that causes symptoms of sneezing, nasal congestion, rhinorrhea, and nasal itch.^{1,2} It is
93 estimated that 10-30% of the population is affected by AR which can have a considerable impact on
94 quality of life (Figure 1).¹ Allergic Rhinitis and its Impact on Asthma guidelines have shown that the
95 severity of symptoms can be measured in clinical practice using a visual analogue scale (VAS), a
96 quantitative tool which can guide decisions on treatment.^{3,4}

97

98 Allergen avoidance and pharmacotherapy, including oral and intranasal H1-antihistamines, intranasal
99 corticosteroids, and leukotriene receptor antagonists are indicated for the treatment of AR (Figure 2).⁵
100 Though subcutaneous immunotherapy (SCIT) has been used for over a century, sublingual
101 immunotherapy tablets (SLIT) are a newer treatment option, that like SCIT, also have
102 immunomodulatory effects on the immune mechanisms that drive AR, thus providing more long-term
103 benefit.⁶

104

105 Currently, there are two types of allergen immunotherapy (AIT): SCIT and sublingual immunotherapy
106 (SLIT). Both administration routes have been shown to be effective for long-term control, and SLIT is
107 increasingly considered to be the safer and more convenient alternative.⁷ SLIT was included as a
108 potential treatment option for adult patients with AR and sensitization to house dust mites with poorly
109 controlled asthma in the 2019 GINA guidelines. SLIT can be administered either via drops (SLIT-D) or

tablets (SLIT-T).⁸ Unlike SLIT-T, evidence supporting the efficacy and optimal dosage of SLIT-D is insufficient, though both have similar safety profiles.⁸ For any immunotherapy, there must be evidence of relevant sensitization.⁹ Once initiated, SLIT is generally taken daily for three to five years, under the supervision of an allergist.⁹ Grass and ragweed SLIT are administered 8 and 12 weeks before the allergy season respectively, and throughout allergy season.⁹⁻¹¹ Grass SLIT is indicated for those aged 5 to 65; ragweed SLIT for those aged 18 to 50⁹⁻¹¹ and house dust mite (HDM) SLIT is administered year-round to those aged 18 to 65.^{9,12} While the product monographs have not been updated online, ragweed SLIT recently received Health Canada and FDA approval for use in the pediatric population (5 y of age and up).

A network meta-analysis (NMA) which included 37 studies (14 SLIT-T, 14 SLIT-D, and 9 SCIT) of 7759 total patients (4016 treated with immunotherapy and 3743 treated with placebo) illustrated that SCIT and SLIT tablets both significantly reduced symptom and medication scores versus placebo.¹³ Authors also performed an indirect comparison between SLIT versus SCIT and found no significant differences for either symptom or medication scores.¹³ However, certain disadvantages were noted to be associated with SCIT, such as the inconvenience of having to attend regular doctor's appointments, uncomfortable injections, followed by 30 minutes of observation.¹⁴ Additionally, while some studies have suggested greater efficacy for AR with SCIT versus SLIT, there are significant limitations involved with these studies and SCIT carries an increased risk of systemic allergic reactions and rare fatality.¹⁵

As research on the efficacy and safety of SLIT continues to evolve, the objective of this review is to describe recent findings pertaining to the use of SLIT-T for AR, one of the most common problems seen in allergy practice.

133

134

135 **DATA SOURCES AND STUDY SELECTIONS**

136 A database search (PubMed.gov) for articles (January 1st, 2016 to February 9th, 2021) was conducted
137 using the following key words: “allergic rhinitis”, AND-ed “sublingual immunotherapy”. Search terms
138 were generated using known terms and synonyms (see e-methods) suggested by allergy specialists.

139

140 **Eligibility Criteria:**

141 The following eligibility criteria were used for article inclusion: Population: Adult and/or pediatric
142 patients with AR with or without conjunctivitis (C). Intervention: Any approach or protocol that involved
143 SLIT-T targeted towards any allergen(s) for the treatment of AR/C. Comparator: Any study irrespective of
144 whether there was a comparator included in the study design. Outcomes: Any studies measuring
145 symptom scores, medication scores, adverse events, and/or adverse drug reactions. Study design:
146 Included were experimental studies (e.g., randomized placebo-controlled trials [RCTs]). Other
147 experimental designs (e.g., non-randomized methods of assignment, controlled before-after studies and
148 interrupted time series), and observational studies (e.g., prospective or retrospective cohort studies,
149 cross-sectional studies, and case-control studies), case reports, opinion-based reports (i.e., editorials,
150 letters and non-systematic or narrative reviews), as well as basic science or animal (non-human subject)
151 studies were excluded.

152

153 **Data synthesis:**

The data were analyzed, and the results were presented in a narrative synthesis. Descriptive tables were prepared to provide an overview of the characteristics of included studies. Since this was not the objective of the manuscript, we did not intend to carry out quantitative analysis, meta-analysis, or assess risk of bias.

RESULTS

A total of 11 randomized placebo-control trials were selected for full-text review and included in the analysis (Table 1).¹⁶⁻²⁶ All studies investigated the use of SLIT on patients with seasonal AR (4 tree pollen studies, 1 grass pollen study, 1 ragweed) or perennial AR (4 HDM studies). One study investigated dual SLIT-T with house dust mite tablets and Japanese cedar pollen tablets.²³

A total of 1895 (665 received placebo) subjects were enrolled in 3 studies that examined the efficacy and safety of Standardized quality (SQ) tree SLIT-T on tree pollen induced AR: 2 birch pollen [BP] and 1 Japanese cedar [JC] pollen.¹⁶⁻¹⁸ Tree pollen-specific IgE antibody levels (≥ 3.5 UA/mL for JC and ≥ 0.70 kU/L for BP Betv1) were consistent inclusion criteria across all three studies.¹⁶⁻¹⁸ Birch pollen studies also required a positive skin prick test (wheal diameter ≥ 3 mm), and Total Nasal Symptoms Scores (TNSS) ≥ 7 (Score Range 0 to 12) prior to enrollment.¹⁸ TNSS is the sum of scores for nasal symptoms including rhinorrhea, congestion, itching and sneezing where each one is measured on a scale from 0 (no symptoms) to a maximum of 3 (severe symptoms).²⁷ One study evaluated the treatment effect of Timothy grass SLIT-T for birch pollen-induced AR in 93 participants (46 received placebo) that were sensitized to both grass and birch pollen using an environmental exposure unit (EEU).²⁵

176

177 One study compared grass pollen allergen SCIT versus SLIT in 106 patients (34 received placebo) with a
178 two-year clinical history of moderate to severe grass-pollen-induced AR; positive skin prick test to grass
179 pollen extract (wheal diameter ≥ 3 mm), grass-pollen specific IgE ≥ 0.7 kU/L, and a total nasal symptom
180 score [TNSS] ≥ 7 .²² Another evaluated the efficacy and safety of ragweed SLIT-tablet (12 Amb a 1-Unit)
181 for up to 28 weeks in 1025 children aged 4 to 17 years (512 received placebo) with AR (Nolte 2020).²⁶

182

183 Our search also yielded 4 house dust-mite induced (HDM) AR studies that included 2,818 patients (1,105
184 received placebo) with moderate to severe HDM-induced AR; HDM-specific IgE ≥ 3.5 kU/L; HDM-induced
185 AR for at least 1 year prior to informed consent, a positive nasal provocation test and with AR symptoms
186 despite having received symptomatic treatment.^{19-21,24} All studies excluded subjects with overlapping
187 seasonal or perennial allergens, a history of moderate to severe, uncontrolled asthma or reduced lung
188 function.^{16-22,24}

189 Another study examined the safety profile and immunological response of dual therapy with SQ HDM
190 and JCP SLIT tablets (administered within 5 min after the other).²³ Patients started on 4 weeks of
191 monotherapy with either SQ HDM (N=54) or JCP SLIT tablets (N=55) followed by 8 weeks of dual
192 therapy.²³

193

194 Symptom scores were primary outcomes in 10 of 11 studies examined, however different scoring
195 systems were used (Table 2). Nine of eleven studies reported significantly lower symptoms scores in
196 treatment groups versus placebo, with the exception of Scadding et al who explored the persistent
197 benefit of 2 years of immunotherapy with grass SLIT or SCIT versus placebo.¹⁶⁻²⁶ After 1 year of

198 discontinuation of treatment (at year 3 follow-up); results showed no significant differences in symptom
199 scores, hence 2 years of immunotherapy of either route was not sufficient to result in persistent benefit
200 after immunotherapy was discontinued.²²

201 By comparison, a study by Gotoh et al showed significant improvement in symptoms scores 15 months
202 after subjects discontinued 2 years of active treatment with Japanese cedar pollen SLIT.¹⁶

203

204 Subgroup analysis of five studies which included children and adolescents (2 tree pollen, 3 house dust
205 mite) showed no statistical difference in symptom scores between children (age 5 to 12 years),
206 adolescents (age 13-17 years) and adults (>18 years) hence showing similar efficacy in all age
207 groups.^{16,17,19-21} In addition, a study by Ellis et al found no treatment effect (no significant changes in total
208 nasal symptom score, total ocular symptom score and total rhinoconjunctivitis symptom score versus
209 placebo) Timothy grass SLIT-T for birch pollen-induced AR.²⁵

210

211 A total of 3 studies compared the safety profile of SLIT in adults versus children and adolescents.^{16,18,21}
212 There were no marked differences in the incidence or severity of adverse drug reactions. The most
213 common adverse events across all seven studies were mild to moderate local site reactions (Table 2).
214 However, Scadding et al reported a higher incidence of treatment related AEs in subjects that received
215 SCIT versus SLIT (64 versus 34 respectively; $P=0.004$).²² Seventeen participants in the SCIT group (47.2%)
216 experienced hypersensitivity episodes (itchy eyes, nose, mouth, throat, sneezing, nasal congestion),
217 following injections versus 1 (2.8%) in the SLIT group (mouth/throat/lip tingling and itching).²² No
218 anaphylaxis was reported in both groups.²²

219

220 Additional secondary endpoints that were measured by the studies in our analysis included quality of life
221 and changes in immunological activity. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a
222 self-administered disease-specific health-related quality of life instrument that measures functional
223 impairments such as sleep disturbance; impairment of daily activities, leisure and/or sport; impairment
224 of school or work; or troublesome symptoms on a 7-point scale (0 = not impaired at all - 6 = severely
225 impaired).²⁸ Higher scores indicate lower quality of life.²⁸ Significant improvement in quality-of-life
226 scores ($P < 0.003$ to $P < 0.001$) were reported in 4 out of 7 studies.^{16,17,20,21}

227
228 Six studies measured antibodies relevant to the process of immunotherapy including allergen-specific
229 IgE and IgG4 (2 birch; 3 house dust mite; 1 grass) at baseline and post-treatment period. Two HDM
230 studies described immunological responses, specifically reporting higher IgE antibody levels at Week 52
231 compared to baseline in the active group versus placebo.¹⁹⁻²¹ Similarly, IgG4 antibodies to *D.*
232 *pteronysinus* and *D. farinae* at Week 52 were higher compared to baseline in the active group but
233 remained unchanged in the placebo group. IgG4 may correlate with the clinical response to
234 immunotherapy. Two studies measured immunological parameters 1 year after discontinuation of
235 treatment.^{16,22} Scadding et al observed subjects with grass pollen allergy who received SCIT and SLIT for
236 two years and after 1-year of discontinuation (at year 3 follow-up visit), found that subjects had a higher
237 allergen specific IgG4 levels with both SCIT and SLIT.²² Furthermore, a study by Gotoh et al (2020)
238 reported increased levels of IgE and IgG4 specific for HDM (*D. farinae*, *D. pteronyssinus*) and JCP after
239 treatment with dual therapy (SQ HDM and JCP SLIT tablets), similar immunological responses to those
240 induced during monotherapy.²³

241

242

DISCUSSION:

Our review of 11 recently published randomized placebo-controlled trials (January 1st 2017 to February 9th, 2021) with 3754 subjects receiving SLIT, reported increased efficacy, safety, immunological parameters and improved quality of life.¹⁶⁻²⁶ Our findings are consistent with a published systematic review of 60 studies with 2333 participants receiving SLIT which found significant reduction in symptoms and medication requirements compared to patients receiving placebo.³⁰

All studies in our review utilized a combination symptoms scores (nasal and conjunctivitis symptoms scores ranging from 0 to 18) and medication scores (use or non-use of antihistamines, corticosteroids; scores ranging from 0 to 20) as a way to measure the efficacy of SLIT-tablets.¹⁶⁻²⁶ As described in other studies, our analysis found different symptom and rescue medication scoring methods across the clinical trials, making it difficult to compare and translate the data to clinical settings.^{30,31} There is no standardized definition of the degree of allergen immunotherapy (AIT) efficacy (combined symptom and medication score).³¹ Studies have shown that the degree of efficacy of AIT is based on the percentage reduction or minimal clinically important difference of symptom and medication scores in the active versus placebo groups over a well-defined period during relevant allergen exposure. The World Allergy Organization (WAO) recommends 20% improvement versus placebo as the “standard” threshold when considering efficacy; whereas the US FDA requires at least a point estimate of 15% difference from placebo with a 95% CI upper limit of at least -10% for the primary endpoint of AIT products.³²⁻³⁵ In the absence of tangible ways to interpret clinical trial efficacy data into every day clinical practice, healthcare providers together with patients will have to decide what other factors of SLIT treatment beyond symptoms scores are important in managing their condition.

266

267 In our review we found the most common adverse events associated with SLIT-tablets were mild
268 to moderate local site reactions and included oral pruritus, throat irritation, ear pruritus, and
269 mouth swelling, all of which rarely needed medical treatment. These findings are consistent with
270 previous studies.^{31,36,37} For real world application of these findings, published guidelines
271 recommend daily use of oral antihistamines for 1 to 2 weeks, if necessary, for patients
272 experiencing mild or moderate local allergic reactions to SLIT. For more severe local swellings,
273 treatment may be discontinued or the next dose can be administered under observation along
274 with oral antihistamine premedication. For patients who experienced local allergic reactions the
275 previous season with SLIT-tablet treatment, oral antihistamines when treatment is reinitiated
276 each season is recommended.³⁸

277

278 None of the studies reported severe adverse events or systemic allergic reactions due to SLIT. The
279 systemic allergic reaction rate for SLIT tablets has been reported between 0.06% and 0.4%.^{39,40} Very few
280 cases of anaphylaxis have been reported with SLIT and to date there have been no fatalities.^{36,38,40,41} A
281 previous review reported 11 cases of nonfatal anaphylaxis out of 1 billion SLIT doses given since 2000.⁴²

282

283 Studies have reported that at least 60% of asthmatics suffer from rhinitis and 20-30% of patients with
284 AR also have asthma.⁴³⁻⁴⁶ All studies in our analysis excluded subjects with moderate to severe,
285 uncontrolled asthma or reduced lung function.¹⁶⁻²⁶ Severe uncontrolled asthma increases the risk of
286 severe systemic allergic reactions and is a contraindication for AIT.^{38,47} The safety and tolerability of
287 ragweed, timothy grass, and HDM SLIT-tablets have been demonstrated in patients with well-controlled
288 and partially controlled allergic asthma.^{40,48,49} Premedication to prevent systemic allergic reactions to

289 SLIT for inhalant allergens has not been fully established. In the United States, the FDA requires a
290 prescription of SLIT-tablets to be accompanied by a prescription for self-injectable epinephrine.^{39,50-52} No
291 other countries with approved SLIT-tablets require an accompanying epinephrine prescription.

292

293 Allergen-specific IgE is a significant serological marker of type 1 hypersensitivity. Immediate reactions
294 involve IgE cross linking by their specific allergens resulting in mast cell degranulation and release of
295 histamine and other inflammatory mediators. IgG4 is thought to exert their anti-inflammatory effect
296 through competitive binding with IgE to the allergen, thereby preventing formation of IgE immune
297 complexes and IgE-mediated activation of mast cells. IgG4 responses require high antigen exposure and
298 are observed during allergen immunotherapy which can result in an increase of IgG4 (10–100 fold), a
299 gradual decline in anti-allergen IgE antibodies (immunologic activity) and consequent symptoms of AR
300 and asthma.⁵³

301

302 Five studies in our review measured changes from baseline in serum levels of allergen specific IgE and
303 IgG4 for all active treatment groups compared to placebo and demonstrated increased immunological
304 activity in subjects that underwent SLIT immediately after treatment and 1 year after
305 discontinuation.^{16,17,19,21,22} Research has shown that changes in allergen specific IgE and IgG levels pre-
306 and post- treatment do not always correlate with clinical efficacy.⁵⁴

307

308 Studies have shown that symptoms of AR have a tremendous impact on patient's quality of life.
309 Four studies reported significant improvement in quality of life scores after receiving SLIT.

310 Patients experience difficulties with sleep, disturbed learning and cognitive functions and
311 decreased productivity at work and school.⁵⁵⁻⁵⁹

312

313 Three studies in our analysis reported efficacy and safety profile of SLIT in adults versus adolescents (12
314 to 17 years old) and children (> 5 years old).^{16,17,20} No significant differences were found. Previous SLIT-
315 tablet trials have demonstrated comparable efficacy between adults and children.⁶⁰⁻⁶³ However, there
316 are unresolved issues on SLIT safety in children such as safety in individuals with moderate to severe
317 asthma, immune deficiency, autoimmune conditions, and oropharyngeal infections.⁶⁴ In addition,
318 practical issues such as how long of an interruption between doses is safe before resuming the usual
319 dose, under which clinical situations should the SLIT dose be temporarily withheld and SLIT use in
320 children less than 4 years old since our included studies reported findings in children age 5 or greater.⁶⁴

321

322 Consideration of immunotherapy and prescribing SLIT should be limited to physicians with
323 adequate training and expertise in the treatment of allergic respiratory diseases. Patients with
324 AR should be referred to an allergist: to identify allergic triggers for rational allergen avoidance,
325 when they experience suboptimal control of their AR symptoms on or side effects from
326 medication and consideration of immunotherapy for effective management.

327

328 Certain gaps in the literature remain especially in the area of prevention of allergic disease, raising many
329 intriguing questions. Further research will be needed to determine whether administering SLIT to
330 sensitized children, with or without atopic dermatitis can prevent the development of atopic dermatitis,
331 allergic rhinitis, asthma and even food allergy; whether SLIT is protective in sensitized children with

positive family histories alone; and for those with already established disease such as food pollen syndrome, whether there is a role for tree pollen SLIT in its treatment.

CONCLUSION:

Current research supports SLIT as a safe and effective treatment that significantly reduces symptoms and medication requirements in AR, with significant improvement in quality of life. Given its safety and efficacy, future developments in the area of prevention may lead to new indications for therapy.

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TABLES

Table 1: Characteristics of included randomized placebo-controlled trials

Study	Study objective	Setting Study Duration	Allergen	Inclusion	Intervention
Gotoh et al 2019 ¹⁶	Optimal dose of Japanese Cedar pollen SLIT tablet Long-term efficacy and safety	41 sites, Japan July 2014-April 2017	Japanese Cedar Pollen	>3.5 UA/mL of JC pollen specific IgE antibody 1 of 3 symptoms (sneezing, runny nose, and blocked nose) for at least 1 week >2 severe symptoms in previous 2 years Excluded: bronchial asthma attack within past 5 years	JC pollen SLIT tablet ALK-Abelló (Hørsholm, Denmark) 1 SLIT tablet daily under tongue for 1 minute, then swallowed First administration by physician; monitor 30 minutes
Biedermann et al 2019 ¹⁷	Efficacy and safety	57 sites Germany, France, Poland, Czech Republic, Denmark, Sweden, Finland, and Russia April 2016-June 2017 Treatment period was 6.5 to 9.5 months	Birch Pollen	Positive skin prick test (wheal diameter, ≥3mm) Bet v 1-specific IgE level (IgE class 2 or greater, >0.7 kU/L) Affected quality-of-life items (sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; or troublesome symptoms) Excluded: Uncontrolled asthma or severe asthma exacerbations	1 SQ tree SLIT-tablet daily ALK-Abello First administration by physician; monitor 30 minutes Subjects treated at least 16 weeks before Tree-pollen season
Couroux et al 2019 ¹⁸	Optimal dose for clinical efficacy	1 site Mississauga, Ontario, Canada; July 2015-April	Birch Pollen	Moderate to severe rhinoconjunctivitis (with or without asthma) Confirmed by medical history	Oral lyophilisate (fast dissolving, freeze-dried formulation) SLIT tablet ALK (Hørsholm, Denmark)

		2016 Treatment period was 24 weeks		Positive skin prick test (wheal diameter, ≥ 3mm) Specific IgE to birch (<i>Betula verrucosa</i>) major allergen 1 (Bet v 1) (≥ 0.70 kU/L)) TNSS Score of ≥ 7 Excluded: uncontrolled asthma, reduced lung function ($FEV_1 < 70\%$), other clinically relevant allergies	1 SQ tree SLIT tablet daily
Okamoto et al 2019 ¹⁹	Efficacy and safety	51 sites Japan October 15–December 2016 52-week study	House Dust Mite	AR symptoms for ≥ 2 years Score of ≥ 3 quantitative analysis of IgE antibody specific to D. pteronyssinus and/or D. farina antigens Positive nasal provocation test RTSS ≥ 6 points/d for 7 days prior randomization Excluded: Symptomatic AR due to allergens other than HDM; mild persistent or more severe asthma	HDM tablets (active) once daily by Stallergenes Greer (Antony, France). Up dosing HDM tablet: Day 1 100IR Day 2 200IR Day 3 to week 52: 300IR

				treatment.	
Okubo et al 2016 ²⁰	Evaluate efficacy and safety	90 sites Japan September 2015 – December 2016 52-week study	House Dust Mite	Moderate-to-severe HDM-induced AR HDM-specific IgE ≥ 3.5 kU/L 1-year medication history of AR Positive nasal provocation tests Excluded subjects with asthma	SQ HDM SLIT tablet (TO-203 [Torii; ALK-Abello, or Merck & Co]) SQ HDM SLIT tablet Doses: 10,000 JAU 20,000 JAU Initial dose 3300 JAU, then up dosed weekly until desired dose reached First administration by physician; monitor 30 minutes 1 SQ HDM SLIT tablet daily
Masuyama et al 2018 ²¹	Efficacy and safety	66 sites Japan July 2015 to November 2016 52-week study	House Dust Mite	Moderate-to-severe HDM AR were HDM-specific IgE ≥ 3.5 kU/L 1-year medication history of AR Positive nasal provocation tests Excluded asthma	SQ HDM SLIT-tablet (TO-203, Torii, Japan; manufactured by ALK, Denmark) daily SQ HDM SLIT- Initial dose 3300 JAU, then up dosed weekly until desired dose reached First administration by physician; monitor 30 minutes

Scadding et al 2016 ²²	Efficacy induced persistent benefit 1 year after discontinuation	1 site United States March 2011-March 2015 4 years	Grass pollen	2-year clinical history of moderate to severe grass-pollen-induced allergic rhinitis - Positive skin prick test to grass pollen extract (wheal diameter ≥ 3 mm), - IgE ≥ 0.7 kU/L - Positive nasal grass allergen challenge (total nasal symptom score [TNSS] ≥ 7 on a 12-point scale). Excluded: overlapping seasonal or perennial allergens, history of moderate to severe or uncontrolled asthma	Sublingual allergen tablet immunotherapy with placebo; Freeze-dried grass pollen (Phleum pratense) sublingual tablets (Grazax [ALK]) Injections, subcutaneous injection immunotherapy (Alutard SQ grass pollen [ALK]) with placebo Double-placebo tablets and injections.
Gotoh et al 2020 ²³	Safety profile and immunological response	14 sites Japan July - December 2018	House Dust Mite and Japanese Cedar Pollen	Positive test IgE specific (≥ 0.7 kU/L) for <i>Dermatophagoides farinae</i> and/or <i>Dermatophagoides pteronyssinus</i> JCP Positive nasal provocation test (house dust) Moderate/ more severe symptoms JCP at least 1 week during both preceding 2 JCP seasons	SQ HDM SLIT tablets (MITICURE®; Torii, Tokyo, Japan; by ALK-Abello, Hørsholm, Denmark) and JCP SLIT tablets (CEDARCURE®, Torii) <i>Study Period 1:</i> first tablet daily sublingually Updose 1 week; maintenance dose 3 weeks. <i>Study Period 2:</i> first tablet sublingually; second tablet administered 5 min of first, maintenance dose 7 weeks. Administration by physician; monitor 30 minutes.
Demoly et al 2016 ²⁴	Efficacy	100 sites	House Dust Mite	Daily total rhinitis symptom score ≥ 6 or 5 with 1 severe symptom at	1 tablet sublingually daily

		12 countries 12 months		baseline For subjects with asthma, daily use of inhaled corticosteroids (ICSs) <400 mg of budesonide or less or equivalent at baseline; allowed increase during study, if needed	SQHDM SLIT-tablet 1:1 mixture extracts from 2 species of HDM (Dermatophagoides pteronyssinus and Dermatophagoides farinae) (ALK) 1:1:1:1 ratio of <i>Der p 1</i> , <i>Der f 1</i> , <i>Der p 2</i> , and <i>Der f 2</i> . First administration by physician; monitor 30 minutes
Ellis et al 2018 ²⁵	Evaluate treatment with Timothy grass SLIT-T on symptoms of birch pollen-induced AR	1 site Canada March 2015 - November 2016	Grass pollen Birch pollen	2-year minimum history both birch pollen-induced and grass pollen-induced seasonal AR - Skin prick test: wheal diameter ≥ 5 mm to both <i>Betula</i> species and <i>Phleum pratense</i> - IgE (sIgE) ≥ 0.7 kU/L; both birch and timothy grass	Timothy grass SLIT-T or placebo taken once daily for 4 months
Nolte et al 2020 ²⁶	Efficacy and safety	80 centres July 2015 - November 2018 Canada, Croatia, Hungary, Serbia, Ukraine, United States	Ragweed	Age 4 to 6: clinical history at least 1 season Age 7 to 17: Clinical history at least 2 seasons Physician diagnosis of AR/C (with or without asthma), Skin prick test: wheal diameter ≥ 5 mm Specific IgE ≥ 0.7 kUA/L	12 Amb a 1-Unit dose of ragweed SLIT-tablet (ALK, Hørsholm) once-daily First dose administered under physician supervision Subsequent doses were self-administered at home Treatment 12 to 20 weeks ragweed pollen season; continued for 8 weeks.

				FEV1 $\geq$ 80% predicted at screening and randomization.	
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523 JAU: Japanese Allergy Units

524 DU: Developmental Units

525 JC: Japanese Cedar

526 JCP: Japanese Cedar Pollen

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528 **Table 2: Key Findings**

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STUDY	N	AGE-RANGE/ MEAN (SD)	PRIMARY ENDPOINT	SECONDARY ENDPOINT	SAFETY
Gotoh et al 2019 ¹⁶	Dose-finding period: 1042 n=260 - at 2000 JAU n=264 - at 5000 JAU n=259 - at 10,000 JAU n=259 - Placebo	5- 64 34.9 (15)	Lower total nasal symptom and medication score (TNSMS) in all treatment groups (P <.0001) Optimal dose: 5,000 JAU	Lower total nasal and ocular symptom and medication score (P<0.001).	No severe AEs AEs mild: • local site reactions • mouth edema • throat irritation • ear pruritus • oral pruritus • oral discomfort
	Long-term administration: 476 Active to active =158 Placebo to placebo = 159 Active to placebo = 78 Placebo to active = 81		Lower TNSMS in all treatment groups	Improved Rhinoconjunctivitis Quality of Life Questionnaire all treatment groups (P < .001)	
Biedermann et al 2019 ¹⁷	634 n=320 Treatment; n=314 Placebo Included 57 adolescents (12 to 17 years old)	12-65 37(14)	Improved total combined score (daily symptom score + daily medication score) (P< .0001)	Improved average total combined score (all P <.0001) Increased IgE and IgG4 antibodies	AEs mild or moderate local reactions Most common AE: • oral pruritus • throat irritation

Couroux et al 2019 ¹⁸	219 55 Treatment 2 DU 54 Treatment 7 DU 54 Treatment 12 DU 56 Placebo	18-65 40 (11.5)	Lower total symptoms score all treatment groups (P<.0001)	No data available	87% reported AEs AEs mild or moderate in severity. Most common AEs: • local site reactions • throat irritation tongue pruritus ear pruritus
Okamoto et al 2019 ¹⁹	422 HDM Tablet (N=205); placebo (N=217)	5-16 10.3(2.7)	Lower average adjusted symptom score and average of daily rhinitis total symptom scores (P=0.0005)	Increased immunological activity (IgE and IgG4 antibodies specific to HDM species) (P<.0001)	97% patients had mild-to-moderate AEs Most common AEs: • Oral pruritus • Mouth edema • Throat irritation • Ear pruritus
Okubo et al 2016 ²⁰	946 313 in 10,000-JAU 314 in 20,000-JAU 319 in Placebo Included 90 adolescents (12 to 17 years old)	12 to 64 26.9 (1.9)	Lower total combined rhinitis scores all treatment groups (P <.001)	Improved Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) all treatments (P=0.003)	AEs mild or moderate Most common AEs: • mouth edema, • oral pruritus • throat irritation.
Masuyama et al 2018 ²¹	458 227 in 10 000 JAU 231 in Placebo	5 to 17 10.8 (2.9)	Lower total combined rhinitis score (P <.001)	Improved Japanese Rhinoconjunctivitis Quality-of-Life Questionnaire (JRQLQ) Increased HDM-specific IgE up to week 12	ADRs were mild or moderate • mouth swelling • stomatitis • throat irritation,
Scadding et al 2016 ²²	106 36 to SLIT tablet with placebo 36 SCIT injections with placebo 34 double-placebo tablets and injections.	18 to 65 33.5 years	No significant differences in nasal allergen induced TNSS in the sublingual immunotherapy or SCIT group from placebo at 3-year follow-up (after 1 year discontinuation) After year 2, improved TNSS AUC both for SLIT and SLIT when compared with placebo	<u>Outcomes at years 1 and 2:</u> • SLIT had decreased use of seasonal rescue medications • Both SLIT and SCIT had decreased early (15-minute) and late (8-hour) skin responses to intradermal allergen challenge • Increased Allergen-specific IgE in SLIT <u>At year 3:</u> • Higher allergen specific IgG4 with both SLIT and SCIT	Adverse events were higher in SCIT group SLIT AEs 22% dyspepsia

Gotoh et al 2020 ²³	109 Monotherapy – 4 weeks; either SLIT tablet: HDM-first group (N=54) JCP-first group (N=55) Dual therapy – 8 weeks; both tablets administered within 5 min of first	6 to 57 22.9 ± 14.4	Occurrences of AEs and ADRs related to drug Hematology and blood biochemistry analyses ≥12 years old, blood collected: screening, randomization, 4, 8, 12 weeks; < 12 years old, blood collected screening only <u>HDM-first group:</u> • Monotherapy - IgE and IgG4 levels (<i>D. farinae</i>) significantly increased from baseline • Dual therapy - JCP specific IgE and IgG4 levels significantly increased <u>JCP-first group:</u> • Trend similar to HDM-first group <i>D. farinae</i> specific IgE week 4 significantly increased, despite not starting dual therapy with SQ HDM SLIT tablet	None	<u>HDM-first group</u> 81.5% AEs 74.1% ADRs <u>JCP-first group</u> 90.9% AEs 78.2% ADRs <u>Monotherapy period:</u> HDM-first group higher ADRs first 3-4 weeks vs JCP-first group <u>Dual therapy period:</u> JCP-first group higher ADRs next 4 weeks vs HDM-first group ADRs: mouth swelling, oral pruritus, throat irritation 3 ADR-related discontinuations
Demoly et al 2016 ²⁴	992 6 SQ HDM SLIT (N=336) 12 SQ HDM SLIT (N=318) Placebo (N=338)	18 to 65 32.3 (10.9)	Total combined rhinitis score TCRS: sum of rhinitis symptom and medication score [range, 0-24] over 8 weeks treatment 6 SQ HDM SLIT Absolute reduction in TCRS=1.18 (P<.002) vs placebo 12 SQ HDM SLIT Absolute reduction in the TCRS=1.22 (P<.001) vs placebo	Significant AR symptom improvement: 6 SQ-HDM (P=0.032) 12 SQ HDM (P=0.003) vs placebo Significant AR medication improvement: 6 SQ-HDM (P=0.008) 12 SQ HDM (P=0.024) vs placebo Significant improvement in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ): 12 SQ HDM (P=0.31) vs placebo Significant improvement Total rhinoconjunctivitis scores 6 SQ-HDM (P=0.011) 12 SQ HDM (P=0.029) vs placebo	Mild AEs reported • oral pruritus, • throat irritation, • mouth edema

Ellis et al 2018 ²⁵	93 N=47 SLIT N=46 Placebo	18 to 65 37.6 (10.7)	No significant changes in total nasal symptom score	No significant changes in total ocular symptom score and total rhinoconjunctivitis symptom score	Mild AEs reported - itchy throat - itchy ears - itchy tongue
Nolte et al 2020 ²⁶	1025 N=513 Ragweed SLIT N=512 Placebo	4 to 17 12.1 (3.2)	Improved total combined symptom and medication score (TCS) during peak season (P<0.001) and entire season (P<0.001) Improved daily symptom score (DSS) and average rhinoconjunctivitis daily medication score improved (both P<0.001)	<u>Asthma subjects:</u> - Improved asthma DSS (P<0.007) - Improved SABA use (P=0.002) and nocturnal awakenings (P=0.017) Specific IgE higher at pre-season visit vs placebo (P < 0.001) Change from baseline IgG4 higher at pre-season and end-of-season vs placebo (P < 0.001).	2% discontinuation due to AEs 13% AEs in 12 to 17 years 5% AEs in aged 5 to 11 years No severe AEs AEs mild: - throat irritation - oral pruritus - ear pruritus

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531 JAU: Japanese Allergy Units

532 DU: Developmental Units

533 AEs: Adverse events

534 SLIT: Sublingual immunotherapy

535 SCIT: Subcutaneous immunotherapy

536 TNSMS: Total Nasal Symptom and Medication Score

537 TCS: Total Combined Symptom and Medication Score

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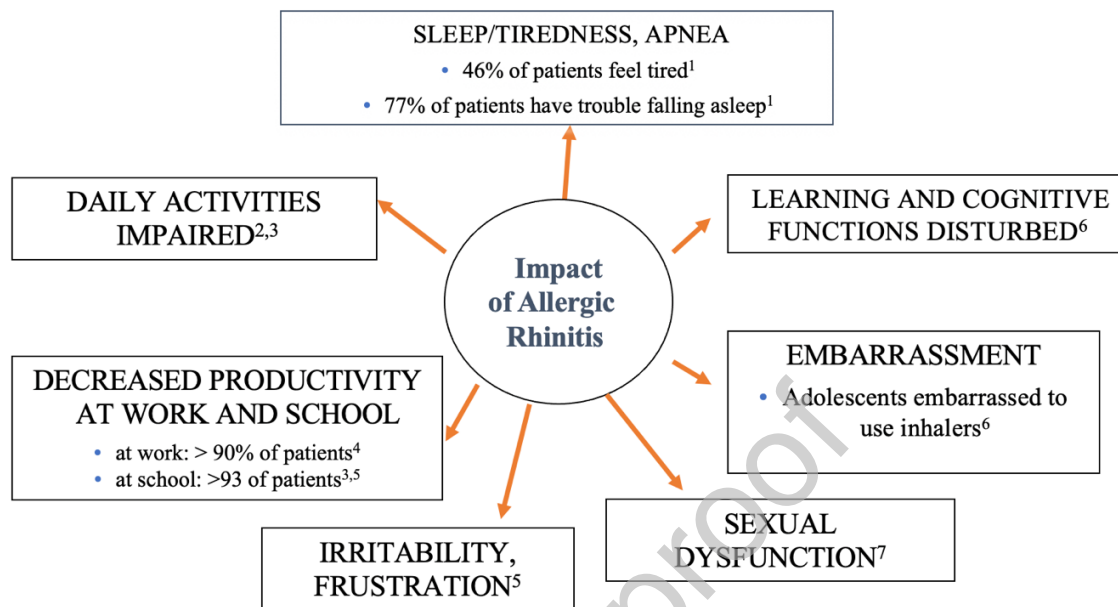


Figure 1. The impact of allergic rhinitis (AR) on patients' daily lives. AR impacts sleep, engagement in daily activities, productivity at work and school, irritability and frustration, sexual dysfunction, embarrassment, and learning and cognitive functions.

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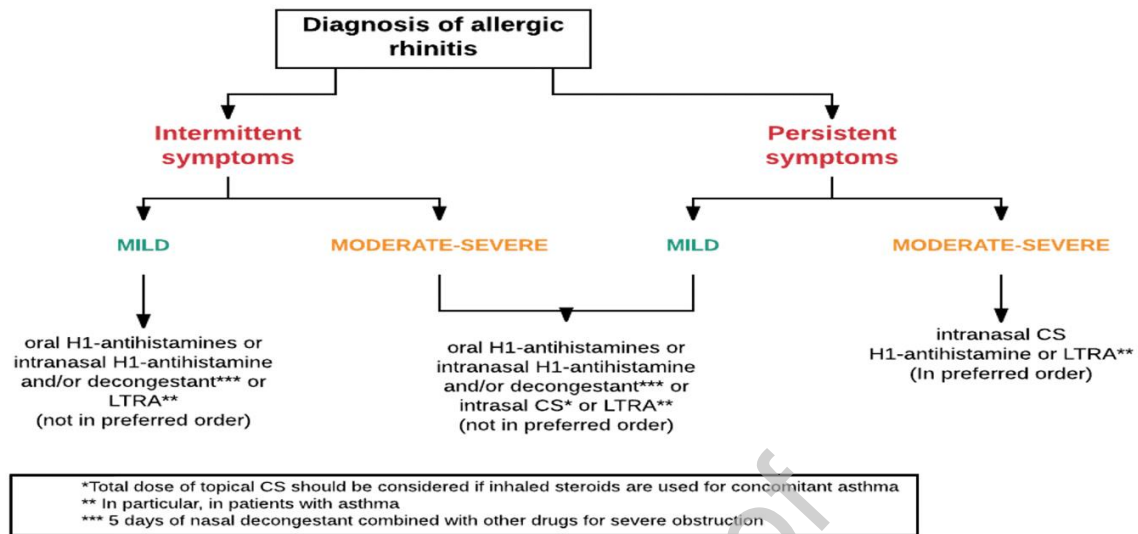
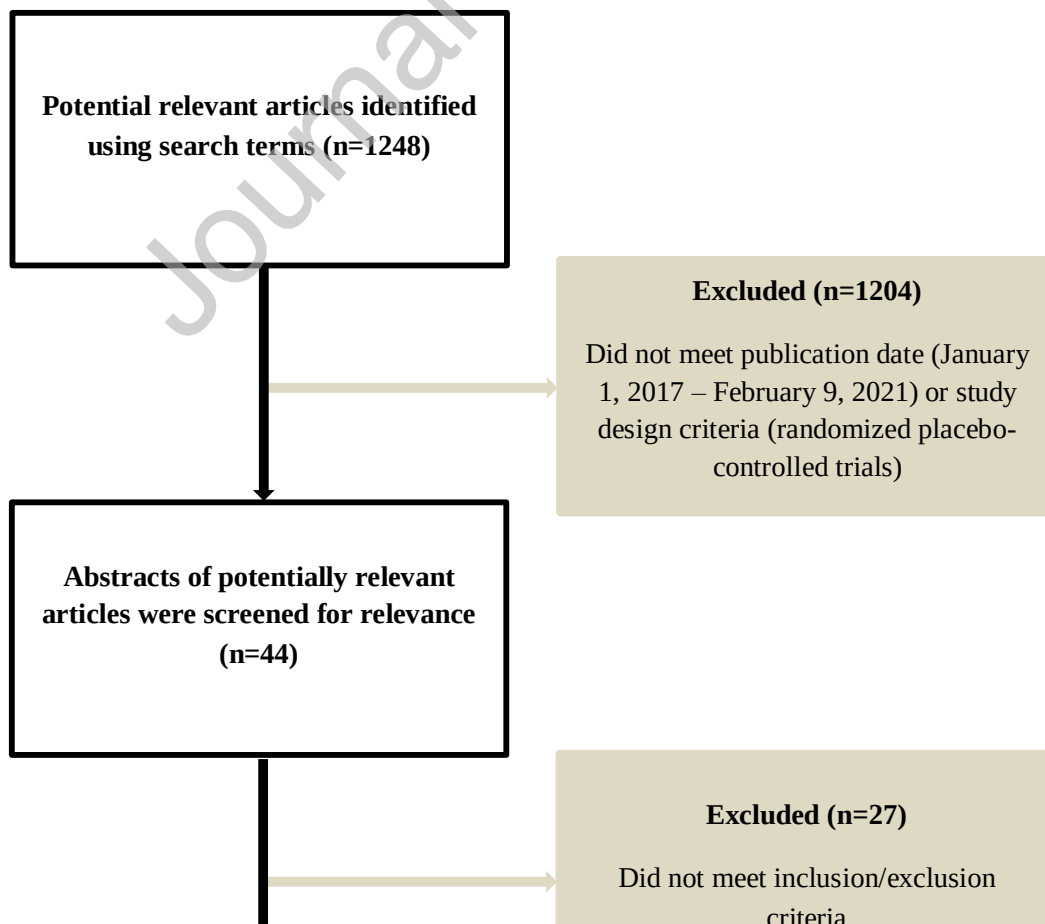


Figure 2. Recommendations around the pharmacotherapeutic treatment of allergic rhinitis (AR), based on Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines.

1. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140(4):950-958.



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Figure 3. Study extraction process. Of 1248 articles identified by our search, 44 abstracts were selected for review on the basis of publication date and study design criteria. Twenty-seven studies that did not meet inclusion and exclusion criteria were removed and eleven studies were selected after full-text review.