Exploring the effect of music therapy in elders living in hospice and palliative care

Annesha Dey Dougherty Valley High School deyannesha22@gmail.com

Abstract

Music therapy is often used in hospice and palliative care of elderly adults and senior citizens nearing the end of their lives. This article discusses the benefits of various types of music therapies in elderly care treatment, including group music therapy (GMT), recreational choir singing (RCS), learning to play an instrument, and musical relaxation techniques. However, though music therapy is being used with increasing frequency in the treatment of those with terminal illnesses, due to the lack of empirical data in the field, many are skeptical of whether external musical therapy can medically improve the condition of terminally ill patients and elders. Thus, this article will also focus on determining the extent to which music therapy improves the mental/physical health and condition of elders living in hospice and palliative care, using existing empirical studies that document evidence-based data. Conclusions establish that though music therapy does not improve the physical condition of terminally ill elders to a significant extent, it does increase their quality of life and mental health in their final days. It further establishes that long-term music therapy and repeated sessions are highly beneficial in hospice and palliative care of elders.

Keywords: music therapy, palliative care, hospice care

Introduction

Music therapy is the clinical use of music interventions that have been shown to provide therapeutic benefits to those living with terminal

illnesses (O'Callaghan C., 2001). Music therapy is an established allied health profession, and music therapists are Board Certified (MT-BC) by the Certification Board for Music Therapists (CBMT) upon the completion of an undergraduate degree and internships/examinations (Mandel S.E., 1993). They help address a variety of healthcare goals, including promoting overall wellness, managing stress, treating memory care patients, promoting physical rehabilitation, etc. (Amy Clements-Cortes, 2004). In elderly hospice/palliative care, musical therapies are offered in various forms; a few of which will be discussed below in addition to the benefits of each.

Dalcroze Method

This method emphasizes the power of physical movement, which therapists typically use to improve physical awareness in patients with significant motor difficulties. It focuses on rhythm, structure, and movement expression, bringing hospice elders to higher levels of musical understanding and movement. Applications of this method include teaching elders how to play musical instruments (Salmon, 1993).

Neurologic Music Therapy (NMT)

This model of music therapy is based on neuroscience and emphasizes the influence of musical perception/production on the brain's functions and behaviors. It is used to instigate brain changes in a patient, for example, training motor responses, etc. Applications of this therapy include listening to live or recorded relaxing music daily (Starr, 1999).

Group Music Therapy (GMT)

GMT is offered by a music therapist and may offer a variety of activities like listening to music, singing, and playing instruments. Emotional processing, which refers to the use of musical interactions to aid in self-reflection, is present in GMT participants (Demmer & Sauer, 2002). This kind of emotional processing may be associated with improved moods and lower rates of depression in older adults. GMT offers social interaction: for example. the one-to-one relationships between group members and the therapist (Gold et al., 2019)

Recreational Choir Singing (RCS)

RCS is typically facilitated by some sort of choir leader and focuses mainly on singing. Cognitive processing, or the learning/memorizing of music pieces, is highly present in RCS. This kind of cognitive processing may maintain cognitive functioning in older adults, specifically those with underlying disorders like dementia. RCS additionally reinforces key social mechanisms; for example, a shared sense of mastery/achievement through group performances of musical pieces (Gold et al., 2019).

Study objectives

- 1. Determine the extent to which music therapy improves the physical condition of elderly hospice/palliative care patients.
- 2. Determine the extent to which music therapy improves the length and quality of life of elderly hospice/palliative care patients.
- 3. Determine the extent to which music therapy improves the mental health of elderly hospice/palliative care patients.
- 4. Determine the extent to which music therapy improves a diagnosed condition like dementia, or reduces the risk of its onset.

Methods

Data from this study comes from ten existing evidence-based studies either published in scholarly journals, or unpublished master's theses. Organized chronologically by date (1993-2019), studies chosen were based on objectives/variables regarding mental and physical health of patients receiving musical therapy. Exclusion criteria is age; all subjects are above 65 years of age. Each study addresses 1 or more objectives listed above: physical condition, quality of life, mental health, or improvement/prevention of diagnosis. This paper will discuss each study's findings and use them to conclude the overall effectiveness of music therapies on elders in hospice/palliative care.

Results

Study 1: Calovini's master thesis on the effect of participation in one music therapy session on state anxiety in hospice patients (Calovini, 1993). 11 adult subjects were observed over the course of 4 months, with eight subjects having been receiving music therapy before the study. All subjects had been diagnosed with some sort of terminal illness. Music therapy was offered through listening and singing along to music, learning to play an instrument, or relaxing with music; each subject was given the option to choose a specific type of therapy. The study utilized various measurements for anxiety, the methods and results of which are listed below:

- 1. Spielberger's State-Trait Anxiety Inventory (STAI) self-reporting questionnaire; data showed no statistically significant differences before and after music therapy sessions
- 2. Physiological measures (systolic/diastolic blood pressure, pulse rate, finger temperature); data showed no statistically significant differences before and after music therapy sessions (Hilliard 2005).

Study 2: Longfield's study on the effects of music therapy on pain and mood in hospice patients (Longfield, 1995).

This quasi-experimental study utilized eight adult subjects in hospice care, all diagnosed with terminal cancer. They received music therapy via taped recordings that they listened to through headsets, for 45 minutes a day for five days. Inferential statistics were used to compare the data difference between pre-test and post-test conditions. The data collection methods and results are listed below:

- 1. Short-Form McGill Pain Questionnaire (SFMPQ)- data showed a statistically significant decrease (P<0.001) in pain
- 2. Linear Analog Self-Assessment Scale (LASA)- scores showed a statistically significant increase in mood from fatigueness and anxiety.

Study 3: Krout's study on the effect of singlesession music therapy interventions on observed and self-reported levels of pain control, physical comfort, and relaxation of hospice patients (Krout, 2001).

90 total sessions were conducted with a total of 80 subjects from Hospice of Palm Beach County, Florida. Five board-certified music therapists provided live music therapy services on a regular schedule. Listed below is the methods of data collection and results regarding patients' levels of pain control, physical comfort, and relaxation before and after each music therapy session:

- 1. Independent observation- used one-tailed t tests; data analysis revealed a significant difference ($P \le 0.001$) for changes in the three dependent variables before and after music sessions.
- 2. Self-reporting: data analysis showed a significant difference ($P \le 0.005$) in the three dependent variables (Hilliard, 2005).

Study 4: Wlodarczyk's study on the effect of music therapy on the spirituality of persons in an in-

patient hospice unit as measured by self-report (Wlodarczyk, 2003)

10 newly admitted adults (n=10), diagnosis, age, or religious preference, participated in this study and had to complete a questionnaire. There were two sessions, A (cognitive-behavioral music therapy) and B (non-music visit). The sessions operated in a 30-minute ABAB pattern for half the participants, and BABA pattern for the other half. The data collection methods and results are listed below:

1. Spiritual Well-Being Scale (SWBS)-18 item questionnaire to measure spirituality; statistical analyses indicated a significant increase in spirituality during music sessions.

Study 5: Hilliard's study on the effects of music therapy on the quality, length of life, and time of death in relation to the last visit of terminal cancer hospice patients (Hilliard, 2003).

In a randomized clinical trial, a total of 80 subjects (n=80) participated in the study and were randomly assigned to either of the two groups: (i) an experimental (receiving routine hospice services and clinical music therapy) or (ii) control (receiving routine hospice services only) group. The study controlled the place of residence to hospice homes, and matched equal numbers of genders and ages to each group. Listed below is the methods of data collection and results regarding patients' length and quality of life, and time of death in relation to the last visit (because music therapists often report that music assists the dying in releasing life):

- 1. Hospice Quality-of-Life Index (HQOLI)- 29-question self-report used to measure changes in quality of life; results showed a significant difference for quality of life for patients receiving music therapy.
- 2. Hospice discipline (nurse, music therapist, etc,)- evaluated time of death relative to the last visit; results showed no statistically significant difference.

Medical record analysis- used to measure length of life; following the subjects' deaths,

with the Hospice Management Systems-Plus software, results showed a statistically significant difference between control and experimental group (Gallagher & Steele, 2001).

Study 6: Takahashi study on the long-term effects of music therapy on elderly with moderate/severe dementia (Takahashi et. al, 2006).

Over the period of 2 years, the long-term effects of a weekly group music therapy on the elderly with moderate or severe dementia was assessed. It was determined by observing changes in the cortisol level in saliva, blood pressure, and by an intelligence assessment. Results from a music therapy group were compared with that of a non-music therapy group. Listed below are the observed the results regarding patients' improvement in dementia:

- 1. Systolic blood pressure determined 1 and 2 years after the start of therapy increased significantly in the non-music therapy group compared with the music therapy group (p< 0.05).
- 2. No significant differences in cortisol level in saliva or intelligence assessment score were observed, but the music therapy group maintained their physical and mental states better than the non-music therapy group during the 2-year period. Results show the lasting effect of continuous music therapy

Study 7: Verghese's study on the effect of leisure activities such as musical therapy and dancing on the risk of dementia in the elderly (Verghese et. al, 2014).

In a prospective cohort of 469 subjects older than 75 years of age who did not have dementia at baseline, cognitive and physical activity was observed using a scale that used activity-days per week as units of measure. Over a median follow-up period of 5.1 years. dementia developed in 124 subjects, Alzheimer's in 61 subjects, vascular dementia in 30, mixed dementia in 25, and other types of dementia in 8. Listed below are the

methods and results regarding the effect of musical activities on the onset of dementia:

1. A one point increment in the cognitive-activity score was associated with a reduced risk of dementia. This association between cognitive activity and decreased risk of dementia was persistent after the exclusion of subjects with preclinical dementia at baseline. Results were similar for Alzheimer's disease and vascular dementia. Increased participation in cognitive activities showed reduced rate of memory decline over the observation period as well.

Study 8: Särkämö's study on the effects of music therapy on the improvement of mental functions in patients with mild-moderate Dementia (Särkämö et. al, 2014).

In a randomized clinical trial, participants with mild-moderate dementia were randomly assigned to a singing group (SG), music listening group (MLG), and a usual care control group. They engaged in this group-based music program for weekly 1.5 hour sessions over the course of 10 weeks. Listed below is the results regarding patients' improvement of mental abilities:

- 1. SG and MLG improved mood, orientation, remote episodic memory, attention, executive function, and general condition.
- 2. SG also improved short-term and working memory.

Study 9: Hsin Chu's study on the impact of group music therapy on depression and cognition in elderly persons with dementia (Chu et. al, 2014). The study utilized a prospective, parallel-group design with permuted-block randomization music. 104 (n=104) older persons with dementia were randomly assigned to either an experimental, receiving 12 sessions of group music therapy (two 30-min sessions per week for 6 weeks), or control group, receiving usual care. Data was collected 4 times- 1 week before treatment, after the 6th session of treatment, after the 12th session of

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FIGURE 1: Study Summaries & Conclusions

	Author	Year	Variables/Objectiv	Methods	Conclusions
#			es		
1	Calovini	1993	Anxiety (mental health)	11 subjects observed for 4 months, with 8 receiving therapy; anxiety levels measured before and after sessions using: • STAI self-reporting questionnaire • Physiological measures (blood pressure, pulse rate, etc.)	1 session is not sufficient for improving health.
2	Longfield	1995	Pain, fatigue, anxiety (physical condition/mental health)	8 subjects observed for 5 days after 45- minute sessions; pain and anxiety levels measured before and after sessions using: • SFMPQ questionnaire for pain • LASA scale for mood	Multiple sessions show higher effectiveness.
3	Krout	2001	Pain, physical comfort, relaxation (physical condition)	80 subjects observed for 90 single- session music therapy interventions on a regular schedule; physical condition measured before and after sessions using: Independent observation Self-reporting	Long term music therapy is effective.
4	Wlodarczyk	2003	Spiritual/Religious well-being (mental health)	10 subjects observed in 2 sessions (A-music therapy and B- non-music therapy), with half in patterns ABAB and half in BABA; spiritual well-being measured after sessions each session using: • SWBS scale	Repeated music therapy sessions are effective.
5	Hilliard	2003	Quality of life	80 subjects observed with half receiving musical therapy and half receiving routine services; length and quality of life observed using: • HQOLI self-reporting questionnaire • Time of death relative to last visit	Length of life unaffected, but quality of life improved.
6	Takahashi	2006	Improvement of severe diagnosed dementia	Moderate/severe dementia elders observed after weekly group music therapy sessions and compared to subjects in non-music therapy sessions; improvement in dementia measured after the start of therapy using: Systolic blood pressure Cortisol level Intelligence assignment	Music therapy is more effective than non-music therapy for dementia patients.

7	Verghese	2014	Risk of illness	469 subjects without dementia observed	There is an
			onset	about 5 years after receiving music	association
				therapy treatment; risk of dementia	between cognitive
				measured using:	activity and
				 cognitive-activity and physical- 	decreased risk of
				activity scales in increment-based	dementia.
				units associated with reduced risk	
8	Särkämö	2014	Improvement of	Subjects with mild-moderate dementia	Music therapy can
			mild diagnosed	observed for 10 weeks in either a singing	increase cognition
			dementia	group, music listening group, or control	in mild patients.
				group; mood and cognitive ability	
				monitored	
9	Hsin Chu	2014	Depression,	104 subjects with dementia received 12	Music therapy
			cognition in	music therapy sessions or control	improves
			dementia patients	sessions, and observed; depression and	depression &
			(mental health)	cognitive function measured after 6th and	cognition.
				12th sessions, and before and after	
				treatment	
10	Murabayas	2019	Depression,	115 subjects observed in either musical	Music therapy
	hi		dementia, social	therapy group or control group for 12	improves mental
			withdrawal	weeks, and then in the other for 12	and physical health.
			(mental/physical	weeks; cognition, physical function, and	
			health)	psychophysical health measured using:	
				VFT Test (cognitive) THO Test (classical)	
				TUG Test (physical) Gardenie Bassassias Casta	
				Geriatric Depression Scale	
				(psychiatric)	

treatment, and 1 month after the final session. Results of the study are listed below:

- 1. Group therapy reduced depression; improvements occurred immediately after music therapy and were apparent throughout the course of therapy.
 - 2. Cognitive function significantly improved after the 6th session, the 12th session, and 1 month after the sessions ended; short-term recall function improved for dementia patients particularly

Study 10: Murabayashi's study on the effects of music therapy in frail elderly patients, age range 65-89 years (Murabayashi et. al, 2019). having one or more care needs regarding social withdrawal, dementia, or depression based on Kihon Checklist (Japanese long-term care insurance system). 115 participants were each

randomly assigned to either a musical therapyfirst group, or a waiting-first group for 12 weeks (first period) and then to the other group for 12 weeks (second period). A 4-week washout period was observed to reduce carryover effects. These 45-50 minute sessions consisted of singing familiar songs, instrumental activities, and physical exercise with music. Methods and outcomes of the study are listed below:

- 1. Cognitive function was measured by the Verbal Fluency Test (VFT); The music therapy-first group showed.
 - 3. Physical function measured by the Timed Up and Go Test (TUG).
 - 4. Psychophysical health measured by the Geriatric Depression Scale 15-item version (GDS-15).
 - 5. Music-therapy periods consistently showed higher levels of improved health across all three categories.

Discussion

In comparing the data provided by the ten empirical studies, a clear link can be established between musical therapy and health benefits in elderly patients in hospice/palliative care. Music therapy is an effective mechanism in end-of-life treatment and care, but to a certain extent. From each of the ten studies, it can be concluded which type of therapy is the most effective. The summary is as follows: (Figure 1)

- 1. Study 1 (Calovini) observing the state of anxiety in hospice care patients showed no statistically significant difference in patient anxiety, blood pressure, pulse rate, finger temperature, etc. before and after a single music therapy session. Thus, it can be concluded that one session alone is limited in its ability to decrease anxiety.
- 2. Study 2 (Longfield) observing pain and mood in hospice patients showed a statistically significant decrease in pain, and a statistically significant increase in mood. This study was conducted over the course of five days, so it can be concluded that multiple music therapy sessions may decrease pain and improve mental health. Study 3 (Krout) supports the use of longterm therapy; it observes pain control, physical comfort, and relaxation across 90 sessions, showing significant improvements in all three variables. Study 4 (Wlodarczyk) supports this as well, this time showing a significant increase in spiritual well-being after multiple 30-minute music Lastly, Study 10 (Murabayashi) sessions. observing improvements in mental and physical health in an elder group treated with long-term further music therapy, corroborates conclusion.
- 3. Study 5 (Hilliard) observing the quality and length of life, as well as time of death in relation to the last visit showed a statistically significant increase in quality and length of life in patients receiving music therapy. However, the data showed no significant difference between the control and experimental groups in terms of

time of death relative to the last visit. Thus, it can be concluded that physical condition can only be improved to a certain extent, given the increase in life length but inconclusive data regarding time of death relative to the last visit.

Study 7 (Verghese) observing prevention of onset of dementia showed a statistically significant decrease in risk of dementia in patients that received music therapy treatment 5 years before. However, though nearly all the subjects eventually developed some type of dementia or related illness, it can only be concluded that musical therapy improves prevention to a small extent. Study 9 (Hsin Chu) Study 8 (Särkämö), observing improvement of patients with mild dementia, both show that music therapy increased cognition more than non-music therapy did in similar patients. Study 6 (Takahashi) observed the improvement of dementia in moderate to severe patients, and showed a statistically significant increase in their cognitive functions.

Conclusion

In summary, music therapy is an efficient therapeutic technique to improve the physical and mental health of elders in hospice and palliative care. Those looking to implement it into the care schedule of any elders can ensure the most efficiency in health improvement by offering therapy sessions on a long-term scale and over time. However, it should be acknowledged that physical health has only been shown to improve in limited amounts, and mental health, stress, and mood improvement should be the main emphasis (Porter et. al, 2017). Additional research is needed to track long term effects of repeated music therapies, specifically those diagnosed with physical terminal mental and illnesses. Drawbacks of these studies include that many measurement tools were not designed specifically for the terminally ill. Further studies are recommended with such tools. Additionally, some studies did not use a large enough sample size to represent the population of elderly, and further

research is needed to establish musical therapy as a legitimate therapeutic practice.

References

Chu, H., Yang, C. Y., Lin, Y., Ou, K. L., Lee, T. Y., O'Brien, A. P., & Chou, K. R. (2014). The impact of group music therapy on depression and cognition in elderly persons with dementia: a randomized controlled study. Biological research for nursing, 16(2), 209–217. https://doi.org/10.1177/1099800413485410

Clements-Cortes A. (2004). The use of music in facilitating emotional expression in the terminally ill. The American journal of hospice & palliative care, 21(4), 255–260. https://doi.org/10.1177/104990910402100406

Clements-Cortés A. (2017). Singing and Vocal Interventions in Palliative and Cancer Care: Music Therapists' Perceptions of Usage. Journal of music therapy, 54(3), 336–361. https://doi.org/10.1093/jmt/thx010 Demmer, C., & Sauer, J. (2002). Assessing complementary therapy services in a hospice program. The American journal of hospice & palliative care, 19(5), 306–314.

https://doi.org/10.1177/104990910201900506

Gallagher, L. M., & Steele, A. L. (2001). Developing and using a computerized database for music therapy in palliative medicine. Journal of palliative care, 17(3), 147–154.

Gallagher, L. M., Lagman, R., Walsh, D., Davis, M. P., & Legrand, S. B. (2006). The clinical effects of music therapy in palliative medicine. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer, 14(8), 859–866. https://doi.org/10.1007/s00520-005-0013-6

Gold, C., Eickholt, J., Assmus, J., Stige, B., Wake, J. D., Baker, F. A., Tamplin, J., Clark, I., Lee, Y. C., Jacobsen, S. L., Ridder, H., Kreutz, G., Muthesius, D., Wosch, T., Ceccato, E., Raglio, A., Ruggeri, M., Vink, A., Zuidema, S., Odell-Miller, H., ... Geretsegger, M. (2019). Music Interventions for Dementia and Depression in ELderly care (MIDDEL): protocol and statistical analysis plan for a multinational cluster-randomised trial. BMJ open, 9(3), e023436. https://doi.org/10.1136/bmjopen-2018-023436

Hilliard R. E. (2003). The effects of music therapy on the quality and length of life of people diagnosed with terminal cancer. Journal of music therapy, 40(2), 113–137. https://doi.org/10.1093/jmt/40.2.113

Hilliard R. E. (2005). Music Therapy in Hospice and Palliative Care: A Review of the Empirical Data. Evidence-based complementary and alternative medicine: eCAM, 2(2), 173–178. https://doi.org/10.1093/ecam/neh076

Kordovan, S., Preissler, P., Kamphausen, A., Bokemeyer, C., & Oechsle, K. (2016). Prospective Study on Music Therapy in Terminally III Cancer Patients during Specialized Inpatient Palliative Care. Journal of palliative medicine, 19(4), 394–399. https://doi.org/10.1089/jpm.2015.0384

Krout R. E. (2001). The effects of single-session music therapy interventions on the observed and self-reported levels of pain control, physical comfort, and relaxation of hospice patients. The American journal of hospice & palliative care, 18(6), 383–390. https://doi.org/10.1177/104990910101800607

Mandel S. E. (1993). The role of the music therapist on the hospice/palliative care team. Journal of palliative care, 9(4), 37–39.

Murabayashi, N., Akahoshi, T., Ishimine, R., Saji, N., Takeda, C., Nakayama, H., Noro, M., Fujimoto, H., Misaki, M., Miyamoto, K., Yamada,

Y., Kohya, I., Kondo, M., Yamaguchi, H., Sasaki, D., & Murai, Y. (2019, March 5). Effects of music therapy in frail elderlies: Controlled crossover study. Dementia and Geriatric Cognitive Disorders Extra. Retrieved September 30, 2021, from https://www.karger.com/Article/FullText/496456.

O'Callaghan C. (2001). Bringing music to life: a study of music therapy and palliative care experiences in a cancer hospital. Journal of palliative

care, 17(3), 155–160.

O'Callaghan C. (2008). Lullament: lullaby and lament therapeutic qualities actualized through music therapy. The American journal of hospice & palliative care, 25(2), 93–99. https://doi.org/10.1177/104990910731013

O'Kelly J. (2002). Music therapy in palliative care: current perspectives. International journal of palliative nursing, 8(3), 130–136. https://doi.org/10.12968/ijpn.2002.8.3.10249

O'Kelly J. (2002). Music therapy in palliative care: current perspectives. International journal of palliative nursing, 8(3), 130–136. https://doi.org/10.12968/ijpn.2002.8.3.10249

O'Kelly, J., & Koffman, J. (2007). Multidisciplinary perspectives of music therapy in adult palliative care. Palliative medicine, 21(3), 235–241. https://doi.org/10.1177/0269216307077207

Porter, S., McConnell, T., Clarke, M., Kirkwood, J., Hughes, N., Graham-Wisener, L., Regan, J., McKeown, M., McGrillen, K., & Reid, J. (2017). A critical realist evaluation of a music therapy intervention in palliative care. BMC palliative care, 16(1), 70. https://doi.org/10.1186/s12904-017-0253-5

Salmon D. (1993). Music and emotion in palliative care. Journal of palliative care, 9(4), 48–52.

Särkämö, T., Tervaniemi, M., Laitinen, S., Numminen, A., Kurki, M., Johnson, J. K., & Rantanen, P. (2014). Cognitive, emotional, and social benefits of regular musical activities in early dementia: randomized controlled study. The Gerontologist, 54(4), 634–650. https://doi.org/10.1093/geront/gnt100

Schmid, W., Rosland, J. H., von Hofacker, S., Hunskår, I., & Bruvik, F. (2018). Patient's and health care provider's perspectives on music therapy in palliative care - an integrative review. BMC palliative care, 17(1), 32. https://doi.org/10.1186/s12904-018-0286-4

Starr R. J. (1999). Music therapy in hospice care. The American journal of hospice & palliative care, 16(6), 739–742. $\frac{\text{https://doi.org/}10.1177/104990919901600612}{\text{https://doi.org/}10.1177/104990919901600612}}$

Takahashi, T., & Matsushita, H. (2006). Long-term effects of music therapy on elderly with moderate/severe dementia. Journal of music therapy, 43(4), 317–333. https://doi.org/10.1093/jmt/43.4.317

Takahashi, T., & Matsushita, H. (2006). Long-term effects of music therapy on elderly with moderate/severe dementia. Journal of music therapy, 43(4), 317–333. https://doi.org/10.1093/jmt/43.4.317

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., Ambrose, A. F., Sliwinski, M., & Buschke, H. (2003). Leisure activities and the risk of dementia in the elderly. The New England journal of medicine, 348(25), 2508–2516. https://doi.org/10.1056/NEJMoa022252