Adherence to tamoxifen in breast cancer patients: What role does the pharmacist play in German primary care?

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Introduction

Breast cancer is the most common cancer in women worldwide. In 2012, nearly 1.7 million new cases were diagnosed.¹ Tamoxifen is commonly used for the treatment of estrogen receptor-positive breast cancer in pre- and postmenopausal women. As a selective estrogen receptor modulator (SERM), tamoxifen acts as an antiestrogen in breast cancer tumors.

The recommended duration of tamoxifen as adjuvant therapy is at least 5 years (daily dose of 20 mg) to reduce the risk of recurrence.² To achieve this treatment goal, therapeutic steady-state plasma concentration of endoxifen (the active metabolite of tamoxifen) should be met.³ Therefore, adherence to daily intake of tamoxifen is crucial.^{4,5}

The World Health Organization has defined adherence as “the extent to which a person’s behaviour corresponds with agreed recommendations from a health care provider.”⁶ Within this definition, the patient is seen as an active partner in therapy.

Ensuring adherence during long-term oral treatment seems to be an unmet medical challenge.⁷ Previous studies showed that adherence to tamoxifen is often suboptimal, ranging from 53% to 86%.⁸ Patients either intentionally interrupted the treatment or unintentionally forgot to take their medication. Several factors associated with suboptimal adherence in tamoxifen treatment have been reported, such as patient-related factors (patient beliefs and knowledge regarding recurrence risk⁹) and therapy-related

factors (duration, side effects¹⁰) and health care system factors (unsatisfactory patient–health care provider relationship¹¹). Poor adherence in long-term treatments can cause poor clinical outcomes and increased health care costs^{12,13} and thus needs to be prevented.

In Germany, tamoxifen is prescribed by the treating physician, usually a gynecologist, in the primary care setting. The prescription is then filled (i.e., the original drug package of the pharmaceutical company is dispensed) by any community pharmacy of the patient’s choice, generally without any specialization. There is also no standardized pharmacist–physician collaboration.

The aim of this study was to assess the impact of health care providers (physicians and pharmacists) on patients’ adherence in Germany, particularly the role of pharmacists within the interdisciplinary team guiding patients’ tamoxifen treatment.

Methods

We conducted a cross-sectional pilot study to analyze patients’, physicians’ and pharmacists’ views on tamoxifen adherence. For this purpose, we developed 3 population-specific questionnaires for breast cancer patients, physicians and pharmacists. The comprehensibility of the questionnaires was piloted with 15 patients, 4 physicians and 5 pharmacists; the questionnaires were revised accordingly.

The study included patients who were on tamoxifen treatment at the time of the study or had been previously treated. Eligible patients

were ≥ 18 years, female and with sufficient written and oral knowledge of the German language. Physicians and pharmacists were included if they stated they were involved in patients' tamoxifen therapy, issued tamoxifen prescriptions or dispensed tamoxifen to patients. Written informed consent was obtained from all participants prior to the survey.

Data collection occurred between August and October 2016. For patient recruitment, 25 gynecological and oncological practices; 6 breast centres; 56 pharmacies in or near Berlin, Germany; and the Berlin chamber of pharmacists were visited. Additionally, online forums and various support groups were contacted to recruit patients. Physicians and pharmacists were addressed via personal contacts in breast centres, gynecological and oncological practices and pharmacies.

The patients' survey was divided into 4 parts: part 1 included questions regarding the patient-physician relationship. Part 2 contained questions regarding the patient-pharmacist relationship. Part 3 focused on assessing patients' experience with tamoxifen therapy, adherence (i.e., number of daily tamoxifen doses intentionally not taken/forgotten in the last months) and reasons for lack of adherence to tamoxifen therapy. Part 4 collected demographic data, tamoxifen treatment duration, therapy setting and the number of regular concomitant drugs.

Physicians' and pharmacists' surveys were divided into 4 parts: parts 1 and 2 contained questions on patients' tamoxifen adherence, suspected factors promoting or hindering adherence, the current situation of adherence management and strategies to improve adherence. Part 3 included questions regarding interactions between pharmacists and physicians about tamoxifen and adherence. Part 4 covered questions regarding a physician's/pharmacist's specialization and the number of his or her regular supervised tamoxifen patients.

Parts of the questions in the 3 surveys were harmonized to allow for comparison between patients', physicians' and pharmacists' answers (Figure 1). For example, all 3 groups were asked these 3 questions adapted to their perspective: 1) "How do you rate (your/the patient's) tamoxifen adherence?" 2) "Do you talk about tamoxifen adherence with your physician or pharmacist/with your patient during consultation?" and 3) "Do you think consultation is a strategy to

increase adherence?" Good adherence was defined as $>80\%$ intake.¹⁴ The questionnaires contained open and closed questions. Responses were allowed as multiple-choice, 5-point Likert scales (never, rarely, occasionally, often, always) and/or free text.

The survey was offered online via the tool "UmfrageOnline" (<https://www.umfrageonline.com>) and paper based. The evaluation was performed anonymously.

Using Microsoft Excel (version 2016), baseline data were presented as percentages or medians (range). The results of the survey questions were described as absolute numbers and/or relative frequencies (%).

Results

A total of 198 patients, aged 32 to 84 years (median: 58.4 years), participated and completed all or more than 2 parts of the survey. Approximately 80% ($n = 161$) of the participating patients were recruited from gynecological and oncological practices. The remaining 20% ($n = 37$) of the participants took part via online forums and support groups.

The response rates of the survey by physicians and pharmacists were 12.9% ($n = 4$) and 28.6%, respectively ($n = 16$).

Adherence

All participating patients reported that they had taken tamoxifen on >24 days within the last month (i.e., $>80\%$). Thus, all patients were considered adherent. The intentional interruption rate of tamoxifen intake was very low: only 1 patient stated that she had not taken her medication for more than 7 days during the previous month.

Participating physicians estimated patients' tamoxifen adherence to be 83%, while pharmacists' estimation was lower, with 72% (Figure 1a).

With respect to persistence, 5 patients (2.7%) stated that they had interrupted their daily intake for more than 5 days. Seven patients (3.8%) completely stopped the therapy (4 of these in agreement with their physician).

Patients stated that suboptimal adherence resulted from unintentionally forgetting the intake (20.5%), especially on weekends/holidays or on busy days, and intentionally interrupting the therapy because of fear of side effects (up to 5.8%). Trust in tamoxifen therapy (80.7%, $n = 155$) was mentioned by patients as the most

FIGURE 1 Excerpt of patient, physician and pharmacist questionnaires and results

common reason for good adherence. Regular treatment consultations were listed by 42.7% patients ($n = 82$) as the second most common strategy for good adherence.

Role in the interdisciplinary team

As the first point of contact to seek medical advice during their tamoxifen therapy, the patients named the physician (81.2%; $n = 121$), the Internet (10.1%, $n = 15$) or support groups/forums (4.70%, $n = 7$). The pharmacist was only named as the second choice after the aforementioned contact points (25%, $n = 23$).

Figure 1b shows that 43.1% of the patients ($n = 85$) talked to their physicians *always to often* about adherence, whereas 33.5% of the patients ($n = 66$) stated *rarely to never*. Of the patients

($n = 142$), 73.6% stated that they take the initiative to ask for information during the consultation. From the perspective of the physicians, nonadherence was addressed *always to often* (75%; $n = 3$) or *rarely to never* (25%; $n = 1$).

According to 77.3% of the patients ($n = 150$), adherence is *rarely or never* a topic during counselling in the pharmacy (Figure 1b). Most pharmacists (66.7%; $n = 10$) confirmed this; 35.9% ($n = 69$) of patients stated that they specifically asked for information in the pharmacy and 71% of patients ($n = 137$) said that the pharmacists offered no consultation at all with respect to their tamoxifen therapy. Figure 1c shows that 43% of the patients ($n = 82$) believe regular follow-ups and therapy consultations would help them to remain adherent. All physicians and 75% of

the pharmacists ($n = 12$) agreed that regular consultations were a good strategy to improve adherence.

In general, attending physicians and pharmacists were *rarely* to *never* in contact with each other (physicians: 100%, $n = 4$; pharmacists: 67%; $n = 10$) (Figure 1d). Patient adherence was *rarely* to *never* a central topic of this exchange (physicians: 100%; $n = 4$; pharmacists: 87%; $n = 13$).

Adherence strategies

More than half of the patients used strategies or tools to manage their medication intake. Most patients (68.1%; $n = 126$) applied cue-dosing (linking the intake with activities of everyday life), while others used reminder devices (19.5%; $n = 36$) like alarm clocks, pill counting (12.4%; $n = 23$) or pillboxes (11.4%; $n = 21$).

Half of the physicians considered the cue-dosing strategy to be useful, while most pharmacists thought reminder devices were a useful strategy to enhance adherence to daily tamoxifen intake.

Moreover, 6 patients independently suggested calendar blisters to improve adherence. One pharmacist also mentioned this strategy.

Discussion

To ensure full adherence of the patient to the tamoxifen treatment, a good and trusting relationship between patients and their health care providers is a key. We conducted a survey to assess patients', physicians' and pharmacists' relationships and roles in the management of tamoxifen treatment and adherence in Germany. Our cross-sectional pilot study showed that patients' self-reported adherence was high. Eight of 10 patients stated that they primarily consult their physician for tamoxifen-related questions. Pharmacists do not seem to play an important role in tamoxifen treatment management in Germany—they were only occasionally/rarely consulted by patients or physicians with respect to this topic. In addition, the pharmacists stated that they do not actively offer consultation and do not see themselves as an important part of the interdisciplinary health care team to support a patient's tamoxifen treatment.

Role of the pharmacist in the interdisciplinary team

Confidence in the therapy motivated most patients (80.7%, $n = 155$) to adhere to daily tamoxifen intake. Regular consultations were the

second most popular reason for increased adherence. Although the pharmacists recognized consultation as a good adherence support strategy, it was surprisingly rarely applied or offered in the pharmacy (and the majority of patients did not think it was important). Only one pharmacist addressed adherence *always* to *often* during his or her consultation. Pharmacists in Germany do not seem to be an active part of the health care team supporting patients' tamoxifen therapy and adherence. Patients preferred to address their tamoxifen treatment-related questions first to their physician, then to the Internet or support groups and forums, and last to pharmacists. According to the patients, pharmacists have not been specifically educated and trained to guide and support their tamoxifen therapy. Therefore, patients did not have any consulting expectations of the pharmacists (25.1%; $n = 37$). A few patients (4.8%; $n = 7$) explicitly stated that "supporting tamoxifen therapy is the task of the physicians." Some (1.4%; $n = 2$) criticized that the privacy in the pharmacy was limited compared to the medical practice. The physicians' perspective on the role of the pharmacist within tamoxifen therapy was diverse. Some physicians felt that pharmacists only have consulting competence in the sale of over-the-counter drugs. Only 1 physician recognized the pharmacist as a valuable partner within tamoxifen therapy, providing important information (e.g., on its appropriate use, drug-drug interactions, adverse events and adherence support). Interestingly, pharmacists themselves considered their role to be "minor" and seemed unwilling to take responsibility for tamoxifen therapy.

Potential perspective for the pharmacist

Pharmacists need to recognize their potential to detect and improve patients' adherence and thus clinical outcomes.¹⁵ Pharmacies can be the first easily accessible contact for tamoxifen therapy guidance: they are frequently visited¹⁶ and no appointments are necessary.

Most pharmacists would be motivated to offer special additional services, such as follow-ups, if reimbursed. Pharmacists could improve their minor role by taking more responsibility for consultation, medication management and therapy support. They should be encouraged to actively and directly offer tamoxifen counselling for the patient and communicate more closely with physicians to improve patients' outcomes. However, the pharmacist, especially in Germany, needs to

raise the awareness of patients, the public and physicians for the pharmacist as a drug specialist.

Pharmacists do need not only knowledge about the medication itself but also communication skills. Therefore, the fundamentals of this competence need to be an essential part of pharmacy training. In Germany, only a few universities offer patient counselling seminars during pharmacy studies. Positive examples are the Medication Management Centre at the Freie Universitaet Berlin¹⁷ and similar projects at university hospitals, for example, in Mainz¹⁸ (initiated by hospital pharmacy) and Bonn¹⁹ (initiated by the Institute of Pharmacy)—creating safe environments for students to acquire knowledge, skills and competence in structured medication reviews, professional communication and long-term medication management, therefore increasing students' ability to promote patients' medication adherence within pharmaceutical care teams.

Apart from detailed counselling on the prescribed drugs, every patient with polypharmacy should have a medication plan. This represents a standardized printout that clearly lists a patient's complete medication, including important information on the drug, the dosing regimen and its application. In Germany, a standardized medication plan has been implemented for patients taking ≥ 3 drugs.²⁰ It is issued by the physician and can be updated by the pharmacist upon agreement with the patient. This overview for patients might be helpful in improving adherence, but further research is needed.²¹⁻²³

In addition, patient-oriented information sheets, including information about the drug, common side effects, possible drug-drug interactions, behaviour in case of missed/incorrect intake and the importance of regular drug intake could be used to support counselling at the counter. Patients would have the opportunity to read the information or call the pharmacy if uncertain. Also, written information has been shown to improve adherence.^{24,25}

Patients' adherence should be monitored to be able to react if inconsistencies occur, which could lead to adverse events. The first step of adherence is collecting the refill of the follow-up prescription by the patient. If this has not occurred, the pharmacist could flag the patient in the system to alert if a refill is due and call the patient if the prescription is not picked up on time. At the time of refill, the pharmacist could offer a follow-up consultation (i.e., inquire how the patients take their medication, if they have

BOX 1 Recommendations

To improve the quality of patient care and to enhance the knowledge of your patients on their medication:

1. Take initiative and be part of the health care team
2. Actively offer consultation
 - Discuss the patient's medication plan (e.g., using the German National Medication Plan)²⁰
 - Provide patient-oriented information sheets
3. Maintain discretion when talking to your patient regularly
4. Include patients in decisions
5. Take your time consulting your patient

any problems with the daily intake or experience adverse effects).²⁶

In addition, from a pharmacoeconomic perspective, medication adherence management is an important "waste-reducing" intervention to save costs²⁷ (and at the same time to improve treatment success). The economic loss due to nonadherence or discontinuation in oral anti-cancer treatment is a topic of current investigations, and cost-containment strategies have been proposed, highlighting the active involvement of qualified health care staff.²⁸

Best-case examples in pharmacy practice show that pharmacists can take an active and responsible role in the care of breast cancer patients. One of them is Melanie Danilak, who initiated pharmacy practice in a multidisciplinary outpatient breast cancer clinic at the Cross Cancer Institute in Alberta, Canada.²⁹

Another example is a community pharmacy in Berlin, Germany, that collaborates with gynecologists and oncologists.³⁰ The pharmacists are specialized in oncology and offer individual patient education, drug interaction checks and structured discussions with the treating physicians on a patient's pharmacotherapy. This best-practice model could serve as a role model for standard of care in Germany.

Overall, to play an active role in patient care, pharmacists must take the initiative to learn about these important therapies and how they can help their patients (this is the hallmark of a professional) (Box 1). As easily accessible health care

providers, they can be the first contact point. To address patients' needs, they should create a private pleasant environment during the consultation by providing discretion and offering enough time.

Challenges and limitations of the performed study

Adherence was reported or estimated by almost all participants as good (>80%). However, it is important to mention that response bias most likely influenced the power of this aspect in the study. Almost 70% of patients were recruited by 1 physician, and presumably patients with a positive attitude towards their medication were more willing to participate. To overcome response bias due to self-reported adherence,³¹ future studies could integrate more objective adherence measurement methods, for example, pill counting or analyzing the prescription data in pharmacies (the actual prescription collection rate).

Currently, no gold standard exists for adherence measurements^{32,33} and no robust factors that reliably predict adherence.³⁴ Thus, measurements of adherence remain a poor estimate of a patient's actual behaviour.

One limitation of this study was the small sample size of health care providers: physicians ($n = 4$) and pharmacists ($n = 16$). Therefore, the results of these 2 populations can only give a first impression, and further studies should focus on them.

Conclusion

The responses from the survey showed that the pharmacist is not yet part of the interdisciplinary team to support and guide tamoxifen therapy in Germany. Thus, to be recognized as a valuable partner within the interdisciplinary health care team, pharmacists need to actively offer consultation and take responsibility for patients' medication management to improve adherence. ■

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Availability of data and materials: The questionnaires (in German language) generated and/or analysed during the present study are not publicly available, but they are available from the corresponding author on reasonable request.

Authors' contribution: LK-S and CK initiated the project. LK-S, MS, SM, SK, LB and CK planned and designed the study. MS, SM and SK conducted the study. LK-S, LB, MS, SK, SM and CK analyzed the data and discussed the results. LK-S and MS wrote the first draft. LK-S, LB, MS, SK, SM and CK reviewed the manuscript. LK-S and CK supervised the project.

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Informed consent: Written informed consent was obtained from all participants prior to the survey.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86.
2. Kreienberg R, Albert US, Follmann M, et al. Interdisciplinary GoR level III guidelines for the diagnosis, therapy and follow-up care of breast cancer. *Senologie* 2013;10:164-92.
3. Madlensky L, Natarajan L, Tchu S, et al. Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. *Clin Pharmacol Ther* 2011;89:718-25.
4. Klopp-Schulze L, Joerger M, Wicha SG, et al. Exploiting pharmacokinetic models of tamoxifen and endoxifen to identify factors causing subtherapeutic concentrations in breast cancer patients. *Clin Pharmacokinet* 2018;57:229-42.
5. Cardoso E, Csajka C, Schneider MP, Widmer N. Effect of adherence on pharmacokinetic/pharmacodynamic relationships of oral targeted anticancer drugs. *Clin Pharmacokinet* 2018;57:1-6.
6. Sabaté E. *Adherence to long-term therapies: evidence for action*. Geneva (Switzerland): World Health Organization; 2003.
7. Martin LR, Williams SL, Haskard KB, DiMatteo MR. The challenge of patient adherence. *Ther Clin Risk Manag* 2005;1:189-99.
8. Huiart L, Ferdynus C, Giorgi R. A meta-regression analysis of the available data on adherence to adjuvant hormonal therapy in breast cancer: a summarizing the data for clinicians. *Breast Cancer Res Treat* 2013;138:325-8.
9. Fagerlin A, Lakhani I, Lantz PM, et al. An informed decision? Breast cancer patients and their knowledge about treatment. *Patient Educ Couns* 2006;64:303-12.
10. Sawesi S, Carpenter JS, Jones J. Reasons for nonadherence to tamoxifen and aromatase inhibitors for the treatment of breast cancer: a literature review. *Clin J Oncol Nurs* 2014;18:E50-7.
11. Liu Y, Malin J L, Diamant AL, et al. Adherence to adjuvant hormone therapy in low-income women with breast

- cancer: the role of provider-patient communication. *Breast Cancer Res Treat* 2013;137(3):829-36.
12. Dunbar-Jacob J. Adherence in chronic disease. *Ann Rev Nurs Res* 2000;18:48-90.
 13. Holman HR. Evidence that an education program for self-management of chronic disease can improve health status while reducing healthcare costs: a randomized trial (abstract). *Assoc Health Serv Res* 1997;14:19-20.
 14. Hansen RA, Kim MM, Song L, et al. Comparison of methods to assess medication adherence and classify nonadherence. *Ann Pharmacother* 2009;43:413-22.
 15. Van't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002;415:530-6.
 16. ABDA-Bundesvereinigung Deutscher Apothekerverbaende e.V. Die Apotheke-Zahlen, Daten, Fakten 2016. Berlin. 1-60 (2016). Available: https://www.abda.de/fileadmin/assets/Pressetermine/2016/TdA_2016/ABDA_ZDF_2016_Brosch.pdf (accessed June 18, 2017).
 17. Bionity.com. Freie Universität first institution in Germany to integrate medication management into the pharmacy study program. Nov. 1, 2016. Available: www.bionity.com/en/news/160321/freie-universitaet-first-institution-in-germany-to-integrate-medication-management-into-the-pharmacy-study-program.html (accessed March 3, 2017).
 18. Klein A, Krämer I, Otto G. Impact of a pharmaceutical care program on liver transplanted patients' compliance with immunosuppressive medication—a prospective, randomized, controlled trial using electronic monitoring. *Transplantation* 2009;87(6):839-47.
 19. Simons S, Ringsdorf S, Braun M, et al. Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. *Support Care Cancer* 2011;19:1009-18.
 20. Bundesministerium für Gesundheit. Das E-Health-Gesetz. 2017. Available: <https://www.bundesgesundheitsministerium.de/themen/krankenversicherung/e-health-gesetz/e-health.html> (accessed June 18, 2017).
 21. Raynor DK, Booth TG, Blenkinsopp A. Effects of computer generated reminder charts on patients' compliance with drug regimens. *BMJ* 1993;1(306):1158-61.
 22. Botermann L, Krueger K, Eickhoff C, et al. Patients' handling of a standardized medication plan: a pilot study and method development. *Patient Pref Adherence* 2016;10:621-30.
 23. Botermann L, Monzel K, Krueger K, et al. Evaluating patients' comprehensibility of a standardized medication plan. *Eur J Clin Pharmacol* 2016;72:1229-37.
 24. Morris LA, Halperin JA. Effects of written drug information on patient knowledge and compliance: a literature review. *Am J Pub Health* 1979;69:47-52.
 25. Deberry P, Jefferies LP, Light MR. Teaching cardiac patients to manage medications. *Am J Nurs* 1975;75:2191-3.
 26. Khandelwal N, Duncan I, Ahmed T, et al. Oral chemotherapy program improves adherence and reduces medication wastage and hospital admissions. *J Natl Compr Canc Netw* 2012;10:618-25.
 27. Bekker CL, Melis EJ, Egberts ACG, et al. Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy. *Res Social Adm Pharm* 2018;pii:S1551-7411(17)30878-1.
 28. Fasola G, Aita M, Marini L, et al. Drug waste minimisation and cost-containment in medical oncology: two-year results of a feasibility study. *BMC Health Serv Res* 2008;8:70.
 29. Beahm NP, Tsuyuki RT. Innovative pharmacy practice: Melanie Danilak. *Can Pharm J (Ott)* 2016;150:14-16.
 30. Berlin Apotheke: Onkologie. 2017. Available: <http://www.berlinapothke.de/unsere-schwerpunkte/onkologie> (accessed June 18, 2017).
 31. Mazor KM, Clauser BE, Yood RA, Gurwitz JH. A demonstration of the impact of response bias on the results of patient satisfaction surveys. *Health Serv Res* 2002;37:1403-17.
 32. Timmreck TC, Randolph JF. Smoking cessation: clinical steps to improve compliance. *Geriatrics* 1993;48:63-66.
 33. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999;21:1074-90.
 34. Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am Rev Resp Dis* 1993;147:1311-20.